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Examining Group 1625
Patent Application
Docket No. GJE-136D1
Serial No. 09/928,139

Doran R. Pace, Patent Attorney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Celia C. Chang
Art Unit	:	1625
Appellants	:	Marianne Langston, Hooshang Shahriari Zavareh
Serial No.	:	09/928,139
Filed	:	August 10, 2001
For	:	Manufacture of Single Isomer Methylphenidate

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

TRANSMITTAL LETTER

Sir:

Enclosed herewith please find Appellants' Appeal Brief Under 37 CFR §1.192 (in triplicate). Please charge the fee of $330.00 to Deposit Account 19-0065.

Any additional fees as required by 37 CFR §1.16 or §1.17 should be charged to Deposit Account No. 19-0065. Two copies of this letter are enclosed for authorization of charges to the Deposit Account.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRP/amh
Attachment: Appeal Brief Under 37 CFR §1.192

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Art Unit	:	1625
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Serial No.	:	09/928,139
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Alexandria, VA 22313-1450

APPEAL BRIEF

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Alexandria, VA 22313-1450 on July 19, 2004.

Doran R. Pace, Patent Attorney

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

This application is owned by Celltech Pharma Europe Limited.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-8 are pending in application Serial No. 09/928,139 (hereinafter the '139 application) and are under final rejection. The final rejection of claims 1-8 is hereby appealed.

IV. STATUS OF AMENDMENTS

No amendments to the claims were filed subsequent to the final Office Action dated December 19, 2003. The claims as currently pending are attached hereto in Appendix A.

V. SUMMARY OF THE INVENTION

The subject invention provides methods for obtaining single enantiomer *d-threo*-methylphenidate or *l-threo*-methylphenidate. Methylphenidate is a therapeutic agent used in the treatment of attention-deficit hyperactivity disorder (ADHD). Methylphenidate contains two chiral centers in the molecule and, therefore, racemic methylphenidate is made up of four separate stereoisomers: *d-threo*-methylphenidate, *l-threo*-methylphenidate, *d-erythro*-methylphenidate, and *l*-

erythro-methylphenidate. Of the four stereoisomers, the *d-threo*-methylphenidate isomer is consider to have the preferred therapeutic activity. A mixture containing both the *d-threo*-methylphenidate and the *l-threo*-methylphenidate stereoisomers can be resolved into the individual *d-threo*-methylphenidate and *l-threo*-methylphenidate stereoisomers using standard resolution methods known in the art, examples of which are described in the subject specification (see page 3, lines 2-6). However, following the resolution step, it is desirable to be able to recycle the unwanted stereoisomer so as to minimize waste and provide for an economically viable process for producing the desired single stereoisomer of methylphenidate. The subject invention provides for recycling of the unwanted stereoisomer based on Appellants' discovery of means to effect racemisation of a single stereoisomer of methylphenidate at both chiral centers of the molecule so as to produce a racemic mixture of all four stereoisomers, which can then be resolved into the individual stereoisomers and the cycle continued. The specification of the '139 application, at page 3, lines 12-20, describes treatment of the unwanted stereoisomer with an acid in order to effect racemization of the unwanted single stereoisomer at both chiral centers of the molecule to produce a racemic mix of all four stereoisomers. A specific embodiment for racemization of the unwanted stereoisomer using a carboxylic acid and heat is described at page 3, lines 13-15, of the subject specification. Methods for resolving enantiomers of methylphenidate using a chiral acid, such as O,O'-ditoluoyltartaric acid, are described at page 3, lines 3-4 and lines 20-21, of the subject specification.

VI. ISSUES

Three issues remain for resolution:

A. Whether the claim to foreign priority under 35 USC 35 §119 will be acknowledged in the subject '139 application.

B. Whether claims 1-8 are unpatentable under 35 USC §103(a) as obvious over any of: 1) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No.

4,254,261); 2) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880); or 3) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880) and Jacques (1981) supplemented with Harris (U.S. Patent No. 6,242,464).

C. Whether the Harris patent (U.S. Patent No. 6,242,464) is disqualified as prior art under 35 USC §103(c) in the rejection under 35 USC §103(a) in which the Harris patent is cited.

D. Whether claim 1 is unpatentable under 35 USC §112, first paragraph, on the grounds that the specification of the '139 application does not enable a person of ordinary skill in the art to make and/or use the claimed invention.

VII. GROUPING OF CLAIMS

Claims 1-8 are rejected under 35 USC §103(a) as obvious over Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261). Claims 1-8 do not stand or fall together under this rejection.

Claims 1-8 are rejected under 35 USC §103(a) as obvious over Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880). Claims 1-8 do not stand or fall together under this rejection.

Claims 1-8 are rejected under 35 USC §103(a) as obvious over Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880) and Jacques (1981) supplemented with Harris (U.S. Patent No. 6,242,464). Claims 1-8 do not stand or fall together under this rejection.

Claim 1 is rejected under 35 USC §112, first paragraph, as nonenabled by the specification of the subject '139 application. Claim 1 stands alone under this rejection.

VIII. ARGUMENT

A. The '139 application is entitled to a claim of foreign priority under 35 USC §119.

In the Office Actions in the subject '139 application, the Examiner has not acknowledged Appellants' claim to foreign priority under 35 USC §119 although such claim was brought to the Examiner's attention in three separate communications to the Patent Office, two of which included a copy of Appellants' formal claim to foreign priority that was originally submitted with the filing of the '139 application. In the Office Action dated December 19, 2003, the Examiner again did not acknowledge Appellants' claim to foreign priority, stating that the "records of filing and claiming such benefit under 35 USC 119 be made of record for [the '139] application." Appellants note that the original priority documents were made of record in the parent application and, pursuant to MPEP §201.14(b), it should not be necessary for Appellants to resubmit the documents from the parent application. However, attached as Appendix B of this Appeal Brief is a copy of Appellants' "Claim of Priority Under 35 USC 119" which was submitted with the filing of the subject '139 application on August 10, 2001. Also attached to the "Claim of Priority Under 35 USC 119" is a copy of the foreign applications, Great Britain application Nos. 9602174.6 and 9618836.2, to which priority is claimed for the subject '139 application. Acknowledgement of Appellants' claim to foreign priority under 35 USC §119 for the subject '139 application is respectfully requested.

B. Claims 1-8 are not *prima facie* obvious over any combination of:

i) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261);

ii) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880); or

iii) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880) and Jacques (1981) supplemented with Harris (U.S. Patent No. 6,242,464).

1. Statement of the rejections under 35 USC §103(a).

Claims 1-8 are unpatentable under 35 USC §103(a) as obvious over a) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261); b) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880); or c) Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880) and Jacques (1981) supplemented with Harris (U.S. Patent No. 6,242,464).

The basis for the rejections on the combination of Shafi'ee *et al.* (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261), as set forth in the Office Action dated September 28, 2001, is quoted below:

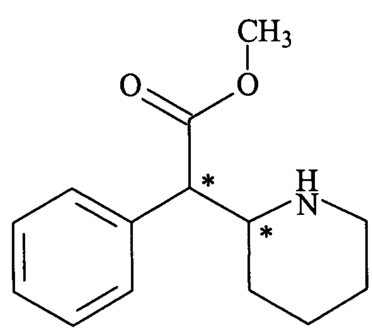
> *Determination of the Scope and Content of the Prior Art (MPEP §2141.02)*
> Shaflee *et al.* disclosed process of making single R,R-threo-methylphenidate (see abstact last three lines).
>
> *Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)*
> Shaflee *et al.* disclosed all the elements of the claim **except** that a further racemization step was not included. Barry taught that in preparation of amino acid esters analogous to the claims, racemization of such ester is achieved under acidic conditions (see acetic acid) and recycling through racemization of the other isomer would give more of the intended isomer (see Miller Ca94 and '261 col. 1 line 64-66).
>
> *Finding of prima facie obviousness-rational and motivation (MPEP §2142-2143)*
> One having ordinary skill in the art is deemed to be aware of all pertinent art in the field. The above references placed the single enantiomer, process of making and alternative choices for increasing single isomeric form in the possession of artisan in the field. It would have been prima facie obvious to employ a conventional modification of Barry or Miller for the conventional process of Shaflee **because** producing higher yield of a desirable isomer is expected which are the attributes taught by prior art.

Based on the combination of references cited, the Examiner concludes that the invention set forth in claims 1-8 would have been obvious to a person of ordinary skill in the art.

2. A *prima facie* case of obviousness has not been established against claims 1-8.

Appellants respectfully assert that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. In order to establish a *prima facie* case of obviousness, the prior art must teach or suggest each and every element and limitation of the claimed invention, and provide a reasonable expectation of success that the modification or combination will succeed. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988). A *prima facie* case of obviousness has not been established against claims 1-8 in the subject '139 application because none of the cited references, either alone or in the combination asserted by the Examiner, teach or suggest each and every element of Appellants' claimed invention, nor do they provide the required reasonable expectation of success.

The claimed invention of the subject '136 application relies on racemization of a single enantiomer of methylphenidate. The product of such racemization is all four possible enantiomers of methylphenidate. Methylphenidate has the following structure, wherein each * represents a chiral center within the molecular structure:



As can be understood from the above structure, methylphenidate has two chiral centers within the molecule. Appellants acknowledge that the primary reference relied upon by the Examiner, Shafi'ee *et al.* (1969), which the Examiner and Appellants have mistakenly referred to as the "Shaflee" reference throughout prosecution of the subject '139 application, discloses methylphenidate;

however, the Shafi'ee *et al.* reference does not teach or suggest methods for racemizing methylphenidate (or any other single molecule with two chiral centers) at both of the chiral centers in the molecule, *i.e.*, wherein every one of the four possible stereoisomers of methylphenidate is produced. The Examiner acknowledged in the Office Action dated September 28, 2001 that the Shafi'ee *et al.* reference does not teach a racemization step. Appellants respectfully assert that none of the other references cited in the rejections under 35 USC §103 teach or suggest methods for racemizing methylphenidate at both of the chiral centers in the molecule. Appellants' discovery and utilization of a means for racemizing methylphenidate at both chiral centers of the molecule is a critical aspect of the invention that the Examiner has apparently failed to appreciate or take into consideration when applying the references cited under the rejections.

Prior to Appellants' invention, there was no teaching or suggestion in the art of being able to racemize methylphenidate at both of the chiral centers of the molecule. This is evidenced by the lack of a reference being cited by the Patent Office specifically teaching the racemization of a single enantiomer of methylphenidate so as to produce all four possible stereoisomers. Appellants assert that none of the references (other than the Shafi'ee *et al.* reference, as acknowledged above) cited by the Examiner under these rejections teach or suggest a single molecule that has two chiral centers within the molecule itself. In making the rejections under 35 USC §103, no evidence or references have been presented or cited by the Patent Office which teach or suggest, with the required reasonable expectation of success, how an ordinarily skilled artisan might effect racemization of a single enantiomer of methylphenidate at both chiral centers of the molecule. The fact that at the time of the subject invention methylphenidate was known in the art and that methylphenidate was known to have two chiral centers does not put the ordinarily skilled artisan in possession of a means for racemizing a single stereoisomer of methylphenidate to produce all four stereoisomers of methylphenidate in the absence of a teaching in the art of a means to effect such a racemization. The Examiner has not indicated where in any of the cited references one can find a teaching or suggestion of a means for racemizing a single enantiomer of methylphenidate (or even an enantiomer of some other molecule having a chemical structure similar to methylphenidate and having two chiral centers) that would have predictably produced all four possible stereoisomers of methylphenidate. Appellants respectfully submit that the Examiner has not indicated where in the cited references one can find the

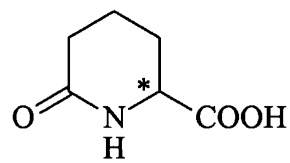
requisite teaching or suggestion because none of the cited references disclose a means for racemizing a single enantiomer of methylphenidate, or a molecule that has two chiral centers and that is structurally analogous to methylphenidate, into all four possible stereoisomers.

The secondary references cited by the Examiner in the Office Actions in the subject '139 application do not overcome the deficiencies of the primary reference. Under each of the obviousness rejections, the Examiner asserted that the Barry reference taught "that in preparation of amino acid esters analogous to the claims, racemisation of such ester is achieved under acidic conditions (see acetic acid)" and that the Miller references taught "recycling through racemization of the other isomer would give more of the intended isomer." The Rometsch patent was cited in the Office Action dated September 28, 2001 as teaching that the "separation of enantiomers can be carried out before or after esterification process" is conventional. The Jacques and Harris references were cited in the September 28, 2001 Office Action as teaching that "continued purification of the product through resolution with a resolving agent" is conventional and operable.

In regard to the Barry reference, Appellants respectfully assert that the amino acid esters (*e.g.*, leucine methyl ester) disclosed in the Barry reference have only **one chiral center** within the molecule itself. Thus, any racemization that may be taught in the Barry reference is racemization of a molecule with a single chiral center, and not racemization of a single molecule with two chiral centers as provided in Appellants' claimed invention. Therefore, the amino acid esters taught in the Barry reference are **not structurally analogous** to methylphenidate and the racemization of such amino acid esters is not analogous to the racemization of methylphenidate. Accordingly, Appellants respectfully assert that the Barry reference does not teach or suggest an individual molecule that has two chiral centers formed by the structural arrangement of the atoms of the molecule and, moreover, does not teach or suggest anything concerning a means for racemizing a molecule, such as methylphenidate, having two chiral centers so as to produce all four possible stereoisomers from a single enantiomer of the molecule.

Appellants also respectfully assert that the compound that is described in the Miller references (abstract (1980) and U.S. Patent No. 4,254,261), homopyrrolidone carboxylic acid (hereinafter referred to as HPCA), has only one chiral center. The HPCA compound, whose

resolution is disclosed in the Miller references, is represented by the following formula, wherein the * represents a chiral center:



Appellants stress that the above compound, like the amino acid esters described in the Barry reference, has only **one chiral center** within the molecule itself. The '261 Miller patent specifically states, at column 1, lines 58-60, that HPCA exists as "the S-enantiomer, the R-enantiomer, and the R,S-racemate." Thus, it is clear from the disclosure in the Miller references that HPCA has one chiral center and, therefore, can exist only as two (not four) enantiomers: R-HPCA and S-HPCA. Dehydroabietylamine (DAA) is a chiral molecule, which is disclosed in the '261 Miller patent as forming a salt with HPCA; however, racemization of DAA is not described in the cited Miller references. Only a racemic mixture of R-HPCA and S-HPCA as free acid, or the mixture of the salts R-HPCA.DAA and S-HPCA.DAA, is described in the cited Miller references. Although a mixture of the salts R-HPCA.DAA and S-HPCA.DAA is formed, the enantiomeric salts (different enantiomers of HPCA; same enantiomer of DAA) are separated. Otherwise, these would be no effective resolution. Moreover, the formation of a salt between HPCA and DAA is not equivalent to a single molecule having two chiral centers, wherein an enantiomer of the single molecule can be racemized to form four separate, distinct stereoisomers.

As noted above, it is only HPCA that is disclosed in enantiomeric forms and it only has a single chiral center. The Miller abstract merely discloses racemizing an enantiomer of HPCA. Specifically, the Miller abstract discloses racemizing either enantiomer of HPCA (referred to therein as the "D" and "L" enantiomers) by heating the enantiomer at 205-250 degrees for a few minutes, followed by resolution of the racemate into D-HPCA and L-HPCA, wherein the L-HPCA was then racemized for recycling into a resolution step. There is no teaching or suggestion in the Miller abstract of racemizing an enantiomer of a molecule that has two chiral centers. In addition, the Miller abstract does not teach or suggest racemization by reacting an unwanted enantiomer with an acid, as is recited in Appellants' claims. Thus, the Miller references do not teach or suggest an

individual molecule that has two chiral centers formed by the structural arrangement of the atoms of the molecule, nor do the Miller references teach or suggest means for racemizing a single enantiomer of a molecule with two chiral centers to give all four different stereoisomers. It is only the disclosure in the subject application that teaches racemization of an enantiomer of methylphenidate into all four stereoisomers.

In addition, the Examiner has not provided any scientific basis to support the assertion in the Office Action dated September 28, 2001 that one would only have to employ a "conventional modification" of [the methods of] Barry or Miller to render Appellants' claimed process obvious. The Examiner has failed to state in the Office Actions what that "conventional modification" is, or why it would be considered "conventional." In establishing a *prima facie* case of obviousness, the burden is on the Patent Office to provide an evidentiary basis for asserting logic and scientific principles in support of the rejection. *In re Grose*, 201 USPQ 57 (CCPA 1979).

In response to Appellants' arguments regarding the failure of the cited references to teach or suggest a means for racemizing a molecule, such as methylphenidate, having two chiral centers within one molecule so as to produce all four possible stereoisomers from a single enantiomer of the molecule, the Examiner stated in the Office Action dated December 19, 2003 that

> Applicant's argument is based on racemization of the "two chiral" center. Please note that **racemization involving two chiral center was disclosed by Miller** see col. 2 **R,S-HPCA.DAA etc. which are material with two chiral center** which are racemized for additional S-enantiomer (see col. 1 line 65-66). Criticality in racemization into "four" enantiomers, thus, is not because of the "two" chiral centers but the conditions employed to ensure all four enantiomers are formed simultaneously. Just because the prior art such as Rometsch did not *name* all four enantiomers, does not mean the racemization using the same acid would not give all four enantiomers. Such can only be obviated by *factual* comparison. (emphasis added)

As an initial matter, Appellants assert that the '261 Miller patent, which the Examiner appears to be referencing in the remarks quoted above, does not teach or suggest methods for racemization of HPCA. Nowhere in the '261 Miller patent is racemization of an enantiomer of HPCA into a mixture of R-HPCA and S-HPCA taught; all of the disclosure in the '261 Miller patent is directed to starting with a racemic mixture, *i.e.*, R,S-HPCA, and resolving the racemate to produce a single enantiomer

of HPCA. Resolution of a racemic mixture to obtain an enantiomer is the opposite of racemization of an enantiomer to obtain a racemic mixture. The only mention of racemization in the '261 Miller patent is at column 1, lines 64-66, where it is indicated that the R-enantiomer of HPCA can be used to produce the S-enantiomer of HPCA upon racemization; however, the disclosure of the '261 Miller patent does not teach how to racemize the R-enantiomer (or the S-enantiomer) to produce a racemic mixture of HPCA. The Miller abstract, as noted in the preceding paragraph, does disclose racemizing an enantiomer of HPCA; however, as is also noted in the preceding paragraph, there is no teaching or suggestion in the Miller abstract of racemizing an enantiomer of a molecule that has two chiral centers. In addition, the Miller abstract does not teach or suggest racemization by reacting an unwanted enantiomer with an acid, as is recited in Appellants' claims.

If one assumes from the Examiner's statement in the December 19, 2003 Office Action "... R,S-HPCA.DAA etc. which are [sic] material with two chiral center ..." that the Examiner is asserting that "R,S-HPCA.DAA" described in the '261 Miller patent is a single molecule having two chiral centers, then Appellants respectfully disagree and assert that the Examiner has not understood the arguments that Appellants have made throughout the prosecution of the subject '139 application. The "R,S-HPCA.DAA" that the Examiner refers to in the '261 Miller patent is **not** a single molecule, but rather is a **salt** composition formed of one molecule of the organic compound HPCA and one molecule of the organic compound DAA. The individual chemical structure of HPCA is shown at column 1, lines 50-58, of the '261 Miller patent and the individual chemical structure of DAA is shown at column 2, lines 1-10, of the '261 Miller patent. Thus, two distinct molecules make up the R,S-HPCA.DAA salt composition. Appellants note that reference is made throughout the '261 Miller patent to the "R,S-HPCA.DAA salt" and that the salts can be converted to the HPCA free acid. Moreover, as noted previously, HPCA has only one chiral center and DAA may have only one chiral center. Furthermore, as Appellants have noted previously, the '261 Miller patent only discloses a racemate of the HPCA molecule itself; the DAA molecule does not undergo racemization.

Appellants respectfully assert that any assumption by the Examiner that the use of racemization methods described in the cited references will result in racemization at both chiral centers of methylphenidate is incorrect. In the Office Action dated December 19, 2003, the

Examiner seems to suggest that all four stereoisomers of methylphenidate are produced from the method of the Rometsch patent but that the Rometsch patent simply "did not *name* all four enantiomers ...." Appellants respectfully assert that one need look no farther than the cited Rometsch patent as evidence that the prior art does not teach or suggest means to racemize methylphenidate at both of its chiral centers. Consideration of the molecular structure of methylphenidate would suggest to the ordinarily skilled artisan that one of the two chiral centers of the molecule can be racemized much more easily than the other, thereby leading to the production of fewer than all four possible stereoisomers. This is clearly supported by the experimental results disclosed in the Rometsch patent. Example 6 of the Rometsch patent discloses epimerisation of methylphenidate with base; however, only one of the two chiral centers of the methylphenidate molecule is racemized, which thereby results in a mixture of diastereomers (*i.e.*, fewer than all of the four possible stereoisomers of methylphenidate are produced). The results disclosed in the Rometsch patent teach that when one started with a single enantiomer of methylphenidate, both chiral centers of methylphenidate were not racemized.

Using the nomenclature of the Rometsch patent, the racemizations described at column 2, lines 19-27, of the patent are:

1) $a_1 + a_2 \rightarrow a_1 + a_2 + b_1 + b_2$,

2) $a_1 \rightarrow a_1 + b_1$

and

3) $a_2 \rightarrow a_2 + b_2$,

wherein

a_1 = *d-erythro*-methylphenidate

a_2 = *l-erythro*-methylphenidate

b_1 = *d-threo*-methylphenidate

b_2 = *l-threo*-methylphenidate.

In reaction (1), the starting materials include two different enantiomers (a_1 and a_2) of methylphenidate and, therefore, racemization is not proceeding from a single enantiomer starting material. In reactions (2) and (3), only two of the four possible enantiomers result from each reaction. It is clear from the Rometsch patent disclosure that these conversions involve "scrambling"

at only one (not both) chiral center of the methylphenidate molecule. Column 2, lines 25-27, of the Rometsch patent confirms this, wherein it is stated that "... **contrary to expectation** the rearrangement in this process takes place at **only one of the two** asymmetrical carbon atoms." (emphasis added). Thus, it is explicitly acknowledged in the Rometsch patent disclosure that racemization of an enantiomer of methylphenidate did not result in racemization at both of the chiral centers of the molecule and, therefore, did not produce all four possible stereoisomers from a single enantiomer of methylphenidate. Accordingly, Appellants respectfully assert that the cited Rometsch patent teaches away from Appellants' claimed invention in that the Rometsch patent specifically discloses that racemization of methylphenidate occurs at only one of the two chiral centers of the molecule and, therefore, Appellants ability to racemize methylphenidate at both chiral centers to thereby produce all four stereoisomers from a single enantiomer of methylphenidate is not taught or suggested.

Moreover, all racemization processes described in the Rometsch patent are in the a→ b direction. In contrast to the teachings of the Rometsch patent, the present invention goes in the opposite direction (b→ a); using the Rometsch nomenclature, either b_1 is racemized (at both chiral centers) or b_2 is racemized (at both chiral centers), to give all of a_1, a_2, b_1, and b_2 (*i.e.*, the four possible enantiomers).

In the Office Action dated December 19, 2003, the Examiner also states in regard to the obviousness rejection of the claims:

> Applicants' attention is drawn to page 4 of the specification wherein the "nature" [sic] process of a single isomer will racemise into four enantiomer was described at lines 5-11 then the instant process of five steps was described wherein the process was the same as those scheme of page 2 that a dl-threo methylphenidate was resolved into single isomers d or l then the l-isomer was racemized. Applicants provided no factual evidence to demonstrate that the **very same** compound of the prior art upon recamization [sic] would *not* give four enantiomers which is the nature [sic] outcome for such compound.

Appellants are not entirely certain what point or argument the Examiner is trying to make concerning the rejection. However, it appears that the Examiner is referring to novel disclosure of the claimed invention in Appellants' own application, and not disclosure concerning the teachings of prior art.

Appellants respectfully assert that the Examiner's statement that "Applicants provided no factual evidence to demonstrate that the very same compound of the prior art upon recamization [sic] would _not_ give four enantiomers which is the nature [sic] outcome for such compound" is not relevant to a determination of the obviousness of the claimed invention because the Examiner has not cited any references which teach or suggest a method for the racemization of a single enantiomer of methylphenidate which results in all four enantiomers being produced. Patent law does not require that an applicant for patent prove the nonobviousness of an invention in the absence of a prior art teaching or suggestion of the invention. The Examiner has not provided any reasoning, explanation or evidence, grounded in scientific principles or logic, that supports the Examiner's position that the production of all four stereoisomers would result from the methods of the Shafi'ee *et al.* reference, the Barry reference, the Miller abstract, the '261 Miller patent, the Rometsch patent, the Jacques reference, or the Harris patent. The Examiner also seems to suggest that Appellants must prove, by way of "factual evidence," that the methods of the cited art do not result in production of all four stereoisomers of methylphenidate. Before the burden shifts to Appellants, the Patent Office must establish a *prima facie* case of obviousness. In establishing a *prima facie* case of obviousness, the burden of providing reasoning or a scientific basis for asserting that the production of all four stereoisomers of methylphenidate occurred in the methods of the cited references lies with the Patent Office, and not with Appellants. *In re Grose*, *supra* at 63 (CCPA 1979) ("When the PTO seeks to rely upon a chemical theory, in establishing a prima facie case of obviousness, [the PTO] must provide evidentiary support for the existence and meaning of that theory."). Regardless, Appellants have established that the references cited by the Examiner, including the Rometsch patent, do not teach or suggest racemization of a single enantiomer of methylphenidate or of a single enantiomer of a molecule that has two chiral centers and is structurally analogous to methylphenidate, such that all four possible stereoisomers are produced by the racemization step.

Appellants also note that dependent claim 8 specifies that the racemization step of claim 1 comprises the use of a carboxylic acid and dependent claim 3 specifies that an achiral carboxylic acid is utilized. Appellants respectfully assert that the references cited under the §103 rejections do not teach or suggest complete racemization of a single enantiomer of a molecule that has two chiral centers using a carboxyclic acid as in claim 8 or an achiral carboxylic acid as in claim 3. In the

absence of a teaching or suggestion in the art to effect complete racemization of the molecule using the claimed acid, a *prima facie* case of obviousness is not established for the claims.

Also attached as Appendix C of this Appeal Brief is a Declaration of Dr. Hooshang S. Zavareh Under 37 CFR 1.132. Appellants also note that Dr. Zarareh's Declaration was submitted with the Amendment dated August 14, 2003 and, therefore, is already of record in the subject '139 application. In his Declaration, Dr. Zavareh points out that racemization of an enantiomer of methylphenidate so that all four enantiomers are obtained requires abstraction of a proton. Dr. Zavareh states that it is, therefore, surprising that an acid, as is recited in the claimed method, could be used to racemize a single enantiomer of methylphenidate into all four possible enantiomers.

In addition, Appellants have also attached as Appendix D of this Appeal Brief an article by Dr. Mahavir Prashad entitled "Approaches to the Preparation of Enantiomerically Pure *(2R,2'R)*-(+)-*threo*-Methylphenidate Hydrochloride" (2001, *Adv. Synth. Catal.*, Vol. 343, No. 5, pp. 379-392). Appellants note that this article was published after the effective filing date of the subject '139 application. Appellants also note that this article was submitted with the Amendment dated August 14, 2003 and, therefore, is already of record in the subject application. The article indicates that the author, Dr. Prashad, is a senior fellow and group leader in the Process R&D section of Chemical and Analytical Development at the Novartis Institute for Biomedical Research. The article is a review article and concerns methods for producing enantiomerically pure methylphenidate. A portion of Dr. Prashad's article (from page 383, section 4) is reprinted below:

> A resolution process is more attractive and economical if the undesired enantiomer can be recycled via racemization. However, in the case of methylphenidate, such a **racemization is challenging** because there are two stereogenic centers which have to be epimerized. A method to affect the racemization at both stereogenic centers has been demonstrated by refluxing a solution of *(2R,2'R)-threo*-methylphenidate (1) with propionic acid in toluene to afford a mixture of four stereoisomers in roughly equal proportions. (citing published International Application No. WO 97/28124) (emphasis added)

First, Dr. Prashad indicates that "racemization [of methylphenidate] is challenging" because there are two chiral centers in the molecule. This is precisely the point that Appellants have argued during prosecution of the '139 application and that the Examiner has failed to appreciate:

racemization of a molecule having two chiral centers so as to produce all four possible stereoisomers is not conventional or obvious. It is the presence of two chiral centers in one molecule that makes complete racemization starting from a single enantiomer "challenging." Dr. Prashad also references published International Application WO 97/28124 as the first publication to describe a successful means for the complete racemization of a single enantiomer of methylphenidate into all four stereoisomers. Dr. Prashad does not reference any other publications as teaching or suggesting a means for racemization of single enantiomer methylphenidate into all four possible enantiomers. Published application WO 97/28124 application, a copy of which is attached with this Appeal Brief as Appendix E, is the corresponding international filing of the subject application. Appellants chose to file an international PCT application (international application No. PCT/GB97/00281, which was published as WO 97/28124) and a separate U.S. utility application (*i.e.*, application Serial No. 08/792,415 filed February 3, 1997, which is the parent application to the subject '139 application) under 35 USC 111 (rather than designating the U.S. in the international application and subsequently filing a national stage application under 35 USC 371). Appellants note that the subject application and the WO 97/28124 application have identical inventorship, claim priority to the same British patent applications, and have the same disclosure in the specification. Thus, Dr. Prashad is, in essence, referencing the subject '139 application as teaching the first successful means for the complete racemization of a single enantiomer of methylphenidate into all four stereoisomers. Accordingly, Dr. Zavareh's Declaration Under 37 CFR 1.132 and the published article by Dr. Prashad provide further evidence as to the nonobviousness of claims 1-8 of the subject application.

The subject '139 application teaches how to racemize a single enantiomer of methylphenidate to produce all four individual enantiomers; this was both novel and nonobvious. The references cited by the Examiner do not teach or suggest how to racemize a single enantiomer of methylphenidate, or any other single molecule having two chiral centers, to produce all four individual enantiomers. In view of the above arguments and evidence presented herein, Appellants respectfully request reversal of all of the rejections set forth under 35 USC §103(a).

C. The Harris patent (U.S. Patent No. 6,242,464) is disqualified as prior art under 35 USC §103(c) in the rejection under 35 USC §103(a) in which the Harris patent is cited.

Appellants note the subject '139 application was filed August 10, 2001 but is entitled under 35 USC §120 to the benefit of the filing date of U.S. parent application Serial No. 08/792,414, filed February 3, 1997, which claims priority under 35 USC §119(e) to U.S. provisional application Serial No. 60/021,135, filed September 12, 1996. Because the subject '139 application was filed after November 29, 1999, it is entitled to the provisions of 35 USC §103(c). The Harris patent (U.S. Patent No. 6,242,464) was filed January 22, 1997 and claims priority to a provisional application filed March 21, 1996. Thus, U.S. Patent No. 6,242,464 <u>only</u> qualifies as prior art against the subject '139 application under 35 USC §102(e). Appellants' undersigned representative previously stated in a clear and conspicuous manner in the Amendment dated August 14, 2003, that "at the time the invention of the subject application was made, the subject application and U.S. Patent No. 6,242,464 were commonly owned by, or subject to an obligation of assignment to, Chiroscience Limited." In the Office Action dated December 19, 2003, the Examiner (apparently in response to Appellants' statement regarding common ownership submitted in the August 14, 2003 Amendment) stated that "the record of [the '139] application is not clear as to "common" ownership as described in the response. Submission of record is required." Appellants respectfully assert that the statement submitted in the August 14, 2003 Amendment is sufficient to disqualify U.S. Patent No. 6,242,464 from being used in a rejection under 35 USC 103(a) against the subject '139 application. In regard to the evidence required to establish common ownership, section 706.02(l)(2), part II, of the MPEP instructs examiners that

> The following statement is sufficient evidence to establish common ownership of, or an obligation for assignment to, the same person(s) or organization(s):
>
> > *Applications and references (whether patents, patent applications, patent application publications, etc.) will be considered by the examiner to be owned by, or subject to an obligation of assignment to the same person, at the time the invention was made, if the applicant(s) or an attorney or agent of record makes a statement to the effect that the application and the reference were, at the time the invention was made, owned by, or subject to an obligation of assignment to, the same person.*

> See "Guidelines Setting Forth a Modified Policy Concerning the Evidence of Common Ownership, or an Obligation of Assignment to the Same Person, as Required by 35 U.S.C. 103(c)," 1241 O.G. 96 (December 26, 2000). **The applicant(s) or the representative(s) of record have the best knowledge of the ownership of their application(s) and reference(s), and <u>their statement of such is sufficient evidence</u>** because of their paramount obligation of candor and good faith to the USPTO.
>
> ... Applicants may, **but are not required to**, submit further evidence, such as assignment records, affidavits or declarations by the common owner, or court decisions, *in addition to* the above-mentioned statement concerning common ownership. (emphasis added)

Thus, the Patent Office's own rules and instructions clearly indicate that further evidence beyond the statement by Appellants' undersigned representative regarding common ownership of the subject '139 application and U.S. Patent No. 6,242,464 in the Amendment dated August 14, 2003 is <u>not</u> required and should have been accepted in the absence of an explanation by the Examiner of a reason to doubt the accuracy of the statement. In regard to the latter, MPEP section 706.02(l)(2), part II, states

> **In rare instances, the examiner may have independent evidence that raises a material doubt as to the accuracy of applicant's representation** of either (1) the common ownership of, or (2) the existence of an obligation to commonly assign, the application being examined and the applied U.S. patent or U.S. patent application publication reference. **In such cases, the examiner may explain why the accuracy of the representation is doubted**, and require objective evidence of common ownership of, or the existence of an obligation to assign, the application being examined and the applied reference as of the date of invention of the application being examined. (emphasis added)

The Examiner in the subject '139 application has not indicated that evidence exists that raises a material doubt as to the accuracy of the statement by Appellants' representative, nor has the Examiner offered an explanation why the accuracy of the statement by Appellants' undersigned representative is in doubt. Therefore, Appellants respectfully assert that the Examiner's refusal to accept the statement regarding common ownership of the subject '139 application and Patent No.

6,242,464 is not in compliance with MPEP 706.02(l)(2) part II. Accordingly, in the absence of an appropriate explanation for not accepting the statement regarding common ownership by Appellants' undersigned representative, Appellants respectfully assert that the statement should be accepted by the Patent Office.

The subject '139 application is a continuation application of U.S. application Serial No. 08/792,415. The inventors assigned their rights in the 08/792,415 application in February of 1997 to Chiroscience Limited. The assignment to Chiroscience Limited in the 08/792,415 application was recorded in the Patent Office on May 1, 1997, at reel/frame: 8483/0885. U.S. Patent No. 6,242,464 was owned by Chiroscience Limited at the time the subject invention was made. Chiroscience Limited is listed as the assignee on the front cover of U.S. Patent No. 6,242,464 and the assignment to Chiroscience Limited was recorded in the Patent Office on April 28, 1997, at reel/frame 8477/0821. Appellants' undersigned representative hereby states again that, at the time the invention of the subject '139 application was made, the subject application and U.S. Patent No. 6,242,464 were commonly owned by, or subject to an obligation of assignment to, the same entity: Chiroscience Limited. Accordingly, under 35 USC §103(c), the subject matter of the Harris patent cannot be used in a rejection of the claimed invention under 35 USC §103(a) and reversal of the rejection set forth under 35 USC §103(a) citing the Harris patent is respectfully requested.

D. Claim 1 is enabled under 35 USC §112, first paragraph.

1. Statement of the rejection under 35 USC §112, first paragraph.

Claim 1 is rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner's explanation of the rejection from the Office Action dated December 19, 2003, is set forth below:

> The specification lacks sufficient description to the instant claims because it is noted that the first step of the instantly claimed process is to resolve *dl-threo*-methylphenidate by the procedure described in the example of PCT/GB97/00185

which is now made of record. Please note that incorporation by reference of essential material is limited to US patent only. Proper incorporation of such material to the specification must be made. The incorporation of material as now amended in the specification has been entered.

The material made by example of PCT/GB97/00185 is the ditoluoyl-D-tartrate salt of *l-threo*-methylphenidate and ditoluoyl-D-tartrate salt of *d-threo*-methylphenidate. No descriptive support can be found as to how such salt is racemized (see p.2 scheme 1) nor was there any descriptive support as to how the two ditoluoyl-D-tartrate salt can be embraced by scheme 1 of the instant specification, or the claimed process.

Further, it is irrelevant arguments presented by applicants as to criticality of how many chiral center when "what" is being made, is it methylphenidate or methylphenidate ditoluoyl-D-tartrate; or "what" is being racemized, is it methylphenidate or methylphenidate ditoluoyl-D-tatrate; were not sufficiently disclosed in the specification.

Under this rejection, the Examiner indicates that International Application No. PCT/GB97/00185 discloses the resolution of *dl-threo*-methylphenidate into a ditoluoyl-D-tartrate salt of *d-threo*-methylphenidate and a ditoluoyl-D-tartrate salt of *l-threo*-methylphenidate and that this disclosure has been incorporated into the specification of the subject '139 application by the Amendment dated August 14, 2003. The Examiner seems to suggest that there is no descriptive support in the subject '139 application for racemization of the ditoluoyl-D-tartrate salts of *d-threo*- and *l-threo*-methylphenidate and no descriptive support as to how the salts can be used in Appellants' claimed invention.

2. A *prima facie* case of nonenablement of claim 1 has not been established.

It is well established that when making a rejection of a claim under 35 USC §112, first paragraph, on the grounds that the specification does not enable the rejected claim, the Patent Office bears "the initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The examiner must also provide evidence or properly reasoned statements in the rejection supporting or explaining the asserted failure to comply with 35 USC §112, first paragraph. *In re Wright*, *supra*.

In the subject '139 application, the Examiner has not provided a reasonable explanation as to why claim 1 is not enabled. Appellants respectfully assert that the rejection, as set forth in the December 19 Office Action, is confusing on its face. As noted above, the Examiner has only indicated that the subject specification does not describe racemization of the ditoluoyl-D-tartrate salts of *d-threo-* and *l-threo*-methylphenidate or how such salts could be used in the claimed process. The Examiner has not set forth any evidence or reasoning as to why a person of ordinary skill in the art would expect that ditoluoyl-D-tartrate salts of *d-threo-* and *l-threo*-methylphenidate could not be racemized or utilized in the claimed process. Accordingly, Appellants respectfully assert that a *prima facie* case of nonenablement of claim 1 has not been established.

3. Methods for the resolution of *dl-threo*-methylphenidate into the *d-threo* and *l-threo* enantiomers are taught in the subject '139 specification and are known to a person of ordinary skill in the art.

Appellants have repeatedly stressed in their written responses to this rejection that the resolution process disclosed in International Application No. PCT/GB97/00185 is but a single example of a resolution process that can be used to resolve *dl-threo*-methylphenidate into the *d-threo* and *l-threo* enantiomers. Resolution using standard procedures, such as by formation of a diastereomeric salt using a chiral acid, is disclosed at page 3, lines 3-4, of the subject '139 application. Many other methods of resolution are known in the art and include, for example, the use of 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate as described in Patrick *et al.* (1987), *The Journal of Pharmacology and Experimental Therapeutics* 241:152-158 and the use of *O,O'*-diaroyltartaric acid as described in International Application No. PCT/GB97/00185, both of which are described at page 1, lines 15-21, of the specification of the subject '139 application.

In addition, as is indicated in International Application No. PCT/GB97/00185, methods for converting the resolving agent salt of methylphenidate (*e.g.*, ditoluoyl-D-tartrate) to the hydrochloride salt via salt exchange procedures are also well known in the art. Accordingly, a person of ordinary skill in the art can readily prepare the hydrochloride salt of methylphenidate for use in the subject invention. Moreover, the free base of methylphenidate can be obtained from a salt

via standard salt cracking methods that are well known in the art. Thus, one can readily prepare a base of methylphenidate from a ditoluoyl-D-tartrate salt of a methylphenidate enantiomer.

It is well settled in patent law that there is no requirement that a specification teach that which is well known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986) citing *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 221 USPQ 481 (Fed. Cir. 1984), ("... a patent need not teach, and preferably omits, what is well known in the art."). The subject specification provides written description and enables the resolution of methylphenidate and salts thereof. In addition, the subject specification provides written description and enables conversion of methylphenidate salts into methylphenidate free base. Accordingly, a person of ordinary skill in the art could readily practice the full scope of Appellants' claimed invention.

Also in the Office Action dated December 19, 2003, under the rejection of claim 1 for nonenablement, the Examiner states the following:

> Based on the disclosure of pages 2-4 the claimed process as delineated in the scheme of page 2 does not required any criticality of how the two chiral center differ from the two chiral center of the prior art compound (please note Rometsch disclosed the same compound, thus, one skilled in the art would know there are the same two chiral center). Applicants provided no factual evidence to demonstrate that the **very same** compound of the prior art upon recamization would _not_ give four enantiomer which is the nature outcome for such compound.

Appellants respectfully submit that it is unclear whether the Examiner's comments are directed to the rejection under 35 USC §112, first paragraph. The above statement by the Examiner appears to be directed to the rejection of the claims under 35 USC §103(a) as obvious over the cited references. However, Appellants will briefly address the Examiner's comments in this section of the Appeal Brief since the comments were associated with the rejection under 35 USC §112.

Appellants' respectfully assert that the presence of the two chiral centers in methylphenidate _is_ a critical aspect of the claimed invention and is _entirely relevant_ to the patentability of the claimed invention. It is stated at page 2, lines 8-9, of the specification of the '139 application that "This invention is based on the discovery of methods to effect racemisation of both chiral centres of methylphenidate." As is noted at page 2, lines 3-6, of the specification of the '139 application, and as has been discussed in detail in this Appeal Brief in regard to the rejections under 35 USC §103(a),

the compounds disclosed in the references cited by the Examiner do not teach or suggest racemization of an enantiomer of a single molecule having two chiral centers wherein all four possible stereoisomers are produced by the racemization. Even the cited Rometsch patent, which Appellants acknowledge discloses methylphenidate, does not teach or suggest a means for racemizing methylphenidate from a single enantiomer. As Appellants have indicated in regard to the obviousness rejection and as is stated at page 2, lines 4-6, of the specification of the '139 application, the Rometsch patent only teaches a process for the production of "a mixture of two diastereomers and not...the racemate that is required for recycling [in the claimed method]." In regard to the Examiner's assertion that Appellants must provide factual evidence that racemization of the compounds disclosed in the cited references would not produce all four enantiomers, Appellants respectfully assert that no such evidence is required because the cited references do not teach or suggest anything concerning a means for racemizing a molecule, such as methylphenidate, having two chiral centers so as to produce all four possible stereoisomers from a single enantiomer of the molecule. The Rometsch patent does not teach or suggest racemization of all four stereoisomers of methylphenidate, and the remaining references do not teach or suggest racemization of an enantiomer of a molecule that has two chiral centers within the atomic structure of the molecule.

In view of the arguments and remarks presented above, Appellants respectfully request reversal of the rejection set forth under 35 USC §112, first paragraph.

In view of the foregoing, Appellants urge that the Board reverse the 35 USC §103(a) obviousness rejections and the 35 USC §112, first paragraph, enablement rejection of record in the subject '139 application and that this application be passed to issuance.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
2421 NW 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRP/sl

Attachments:
Appendix A: Currently Pending Claims
Appendix B: Copy of Appellants' Claim of Priority Under 35 USC 119
Appendix C: Declaration of Dr. Hooshang S. Zavareh Under 37 CFR 1.132 dated July 15, 2003
Appendix D: Copy of published article by Mahavir Prashad (2001)
Appendix E: Copy of Published International Application WO 97/28124

APPENDIX A

Currently Pending Claims

1. A process for obtaining single enantiomer *d-threo*-methylphenidate or *l-threo*-methylphenidate, which comprises resolution of a mixture of the *d-threo*-methylphenidate and *l-threo*-methylphenidate enantiomers; racemisation of the unwanted enantiomer, to give a mixture of all four stereoisomers, wherein the racemisation comprises reacting the unwanted enantiomer with an acid; enriching said mixture following racemisation wherein the *d-threo* and *l-threo* stereoisomers of methylphenidate are enriched over the *d-erythro* and *l-erythro* stereoisomers of methylphenidate; and separation of said *d-erythro* and *l-erythro* stereoisomers, to leave the said mixture of *d-threo*-methylphenidate and *l-threo*-methylphenidate enantiomers for resolution.

2. The process, according to claim 1, wherein the single enantiomer obtained is the *d-threo* isomer, *i.e.*, the isomers of (*R,R*) absolute configuration.

3. The process, according to claim 1, wherein the racemisation comprises heating the unwanted enantiomer with an achiral carboxylic acid.

4. The process, according to claim 1, wherein the separation is conducted following hydrolysis of the mixture of stereoisomers, to give ritalinic acid, and before or after re-esterification of the acid.

5. The process, according to claim 4, which additionally comprises equilibrating the product of hydrolysis wherein the *threo* diastereoisomer is preferentially obtained.

6. The process, according to claim 1, wherein the resolution is conducted using a chiral acid.

7. The process, according to claim 6, wherein the acid is *O,O'*-ditoluoyltartaric acid.

8. The process, according to claim 1, wherein the racemisation comprises heating the unwanted enantiomer with a carboxylic acid.

APPENDIX B

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on June 4, 1997.

David Saliwanchik

David R. Saliwanchik, Patent Attorney

Patent Application
Docket No. GJE-136
Serial No. 08/792,415

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	:	(not yet assigned)
Applicant(s)	:	Marianne Langston, Hooshang Shahriari Zavareh
Serial No.	:	08/792,415
Filed	:	February 3, 1997
For	:	The Manufacture of Single Isomer Methylphenidate

Assistant Commissioner for Patents
Washington, D.C. 20231

CLAIM OF PRIORITY UNDER 35 U.S.C §119

Sir:

Applicants hereby reaffirm their claim to the right of priority granted pursuant to 35 U.S.C. §119 based upon Great Britain application Serial No. 9602174.6, filed February 2, 1996 and Great Britain application Serial No. 9618836.2, filed September 10, 1996.

As required by the Statute, a certified copy of each of the above Great Britain applications is being submitted herewith.

Respectfully submitted,

David Saliwanchik

David R. Saliwanchik
Patent Attorney
Registration No. 31,794
Phone No.: 352-375-8100
Address : 2421 N.W. 41st Street
Suite A-1
Gainesville, FL 32606

DRS/mjc
Attachment: Certified copy of priority documents 9602174.6 and 9618836.2

The Patent Office

The Patent Office
Cardiff Road
Newport
Gwent
NP9 1RH

e undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) ie Deregulation and Contracting Out Act 1994, to sign and issue certificates on behalf ie Comptroller-General, hereby certify that annexed hereto is a true copy of the ments as originally filed in connection with the patent application identified therein.

cordance with the Patents (Companies Re-registration) Rules 1982, if a company named s certificate and any accompanying documents has re-registered under the Companies 980 with the same name as that with which it was registered immediately before re- ation save for the substitution as, or inclusion as, the last part of the name of the "public limited company" or their equivalents in Welsh, references to the name of the ny in this certificate and any accompanying documents shall be treated as references name with which it is so re-registered.

I rdance with the rules, the words "public limited company" may be replaced by p.l.c., L.C. or PLC.

R stration under the Companies Act does not constitute a new legal entity but merely s the company to certain additional company law rules.

Signed

Dated 20 JAN 1997

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The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

Request for the grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference — REP05155GB — 2 FEB 1996

2. Patent application number *(The Patent Office will fill in this part)* — **9602174.6**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   <u>Chiroscience Limited</u>
   Cambridge Science Park
   Milton Road
   Cambridge
   CB4 4WE
   United Kingdom

   Patents ADP number *(if you know it)* — 6536684001

   If the applicant is a corporate body, give the country/state of its incorporation — GB

4. Title of the invention

   RESOLUTION/RACEMIZATION PROCESS

5. Name of your agent *(if you have one)*

   GILL JENNINGS & EVERY

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   Broadgate House
   7 Eldon Street
   London
   EC2M 7LH

   Patents ADP number *(if you know it)* — 754002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

   YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	3
Claim*(s)*	2
Abstract	
Drawing*(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. For the Applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date 2 February 1996

12. Name and daytime telephone number of person to contact in the United Kingdom

PERRY, Robert Edward
0171 377 1377

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

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Resolution/racemization process

Field of the Invention

This invention relates to an economic process for the manufacture of a single isomer of methylphenidate through combining resolution with recycling of the undesired enantiomer.

Background to the Invention

Methylphenidate was first prepared as a mixture of the *erythro* [*R***S**] and *threo* [*R***R**] racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereoisomer.

The resolution of *threo* methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, a process first reported by Patrick et al (*The Journal of Pharmacology and Experimental Therapeutics*, 241: 152-158 (1987). Recently we have discovered a more efficient resolution with *O,O'*-diaroyltartaric acid (British Patent Application PCN0123) and in particular *O,O'*-di-*p*-toluoyltartaric acids where the diastereoisomeric salts are very readily separated. In general it is the d-*threo* [or (*R,R*)] enantiomer that is considered to have the preferred therapeutic activity.

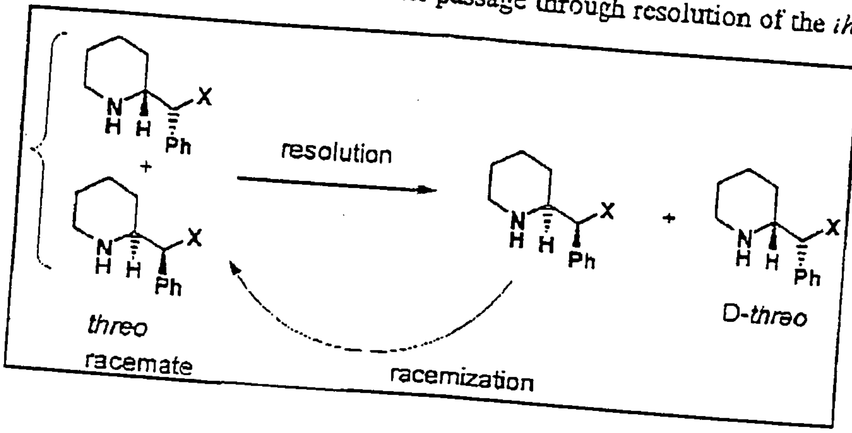
In an alternative approach disclosed in US-A-2957880, the amide of *erythro* methylphenidate (i.e. as $-CONH_2$ instead of $-CO_2Me$) is resolved with tartaric acid. Then amide hydrolysis, and equilibration at the benzylic centre gives the *threo* isomer of the carboxylic acid which is esterified.

In order to establish an economic resolution process, it is highly desirable to be able to recycle the unwanted enantiomer into the resolution by way of a racemization. This becomes especially important when the resolution is performed late in a synthesis. An example of such a resolution and racemization procedure is the case of naproxen where the single stereogenic carbon centre, which is benzylic and further activated by the carboxylate, is readily racemized. However, in the case of methylphenidate, there are two stereogenic centres. While one centre is similarly benzylic and can be epimerized as indicated in US-A-2957880, that converts the material into a mixture of diastereoisomers and not into the racemate that is required for recycling. There is no method reported by which epimerization of the stereogenic centre adjacent to the piperidine nitrogen atom in methylphenidate can be effected.

Description of the Invention

This invention is based on the novel discovery of methods to effect epimerization of *both* chiral centres in methylphenidate. Such epimerization gives a thermodynamic mixture of isomers, and given that the equilibrium favours the *threo* isomer, the result is that undesired enantiomer is converted predominantly into the racemate of the *threo* isomer which can then be reinput into the resolution. The overall process of a combination of resolution and racemization allows complete conversion into the required isomer is outlined in Scheme 1. The minor amount of *erythro* isomer that may remain after the racemization can be separated by conventional methods

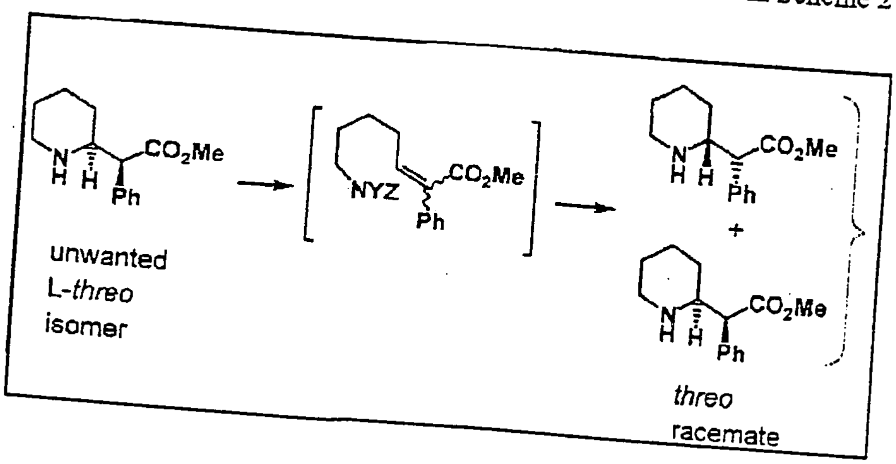
such as crystallization at this stage and subjected further to the epimerization conditions defined below. Alternatively, it can be recycled after passage through resolution of the *threo* isomer.



Scheme 1

In Scheme 1, the group X may be the -CO_2Me function of methylphenidate and resolution carried out as known through formation of a diastereoisomeric salt with a chiral acid. Alternatively the group X may be a different ester, an amide, or a nitrile which can be converted into the methyl ester for methylphenidate. The resolution may be a biotransformation that modifies the group X in one enantiomer so that the enantiomers are then separated.

The invention is the racemization which requires epimerization at both stereogenic centres. We have discovered that such racemization can be carried out by way of activation at the piperidine nitrogen to promote a fragmentation of the ring. The resultant olefinic intermediate has no chirality and recloses to a racemic mixture. The mechanism is shown in Scheme 2 for the case of methylphenidate itself.

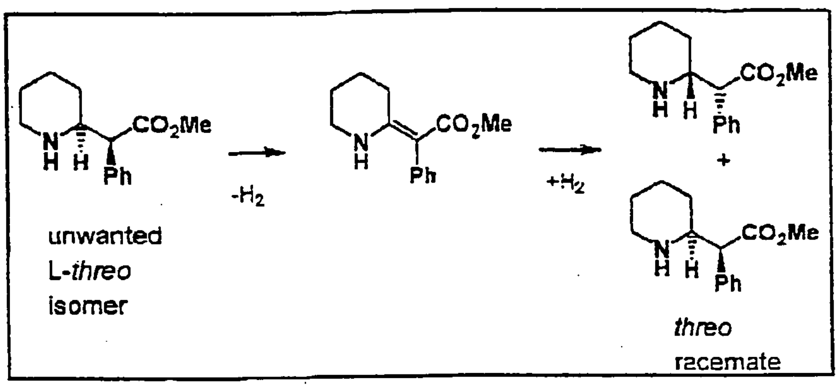


Scheme 2

There are several ways in which the nitrogen could be activated to promote the elimination-addition mechanism. One approach is treatment with an acid, for example a carboxylic acid, at a sufficiently high temperature, such as heating with propionic acid under reflux. This racemization can optionally be accelated by addition of judicial amounts of additives such as water or inorganic salts that will favour the charge separation in the transition state of the elimination. In another method, treatment with an aldehyde or ketone (e.g butyraldehyde or 2-

cyclohexen-1-one) forms an iminium ion which as well as activating the elimination, could render the proton at the piperidine stereogenic centre sufficiently acidic to be removed by a base present. Thus a typical procedure involves heating the unwanted enantiomer with an aldehyde and a base in an appropriate solvent. A further approach is to first acylate the nitrogen atom to activate it as a leaving group for the acylation, though that has the disadvantage that extra steps are required to add and remove the acyl function.

An alternative strategy for effecting racemization of the undesired isomer is by a dehydrogenation/hydrogenation sequence as depicted by Scheme 3. The procedure may be effected either stepwise or catalytically. Thus for example, the dehydrogenation could be by way of bromination at the benzylic position followed by dehydrobromination to the olefin; then this olefin hydrogenated. In this sequence it is likely that the geometric isomer of the olefin indicated in Scheme 3 will be formed in preference because of the stabilisation of having the nitrogen and ester function in a *trans* relationship. In that event, the usual *cis* hydrogenation will give the required *threo* diastereoisomer of methylphenidate. In a catalytic procedure, a catalyst is chosen that will remove and then reattach hydrogen. A heterogeneous catalyst such as a transition metal adsorbed on carbon or a homogeneous catalyst such as a phosphine complex of ruthenium or rhodium could be effective.



Scheme 3

Claims

1. A process for obtaining a single enantiomer of *threo* methylphenidate which combines resolution with racemization of the unwanted enantiomer.

2. A process according to Claim 1 where the enantiomer obtained is the d-*threo* isomer [i.e. the isomer of (*R,R*) absolute configuration].

3. A process according to Claims 1 or 2 where the racemization of unwanted enantiomer is effected by heating with a carboxylic acid.

4 A process according to Claims 1 or 2 where the racemization of unwanted enantiomer is effected by the addition of an aldehyde or ketone.

5. A process according to Claims 1 or 2 where the racemization of unwanted enantiomer is effected by way of acylation of the piperidine nitrogen nitrogen then acid or base treatment.

6. A process according to Claims 1 or 2 where the racemization of unwanted enantiomer is effected by way of dehydrogenation to the olefin shown in Scheme 3 then hydrogenation.

7. A process according to Claim 6 where the dehydrogenation step is effected by way of halogenation then dehydrohalogenation.

8. A process according to Claim 7 where the halogen is bromine.

9. A process according to Claim 6 where the dehydrogenation and hydrogenation is effected by means of a catalyst that can remove and re-add hydrogen to to the substrate.

10. A process according to Claim 9 where a heterogeneous catalyst is used based on a transition metal or transition metal oxide.

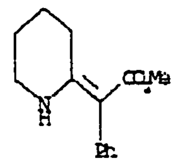
11. A process according to Claim 9 where a homogeneous catalyst is used based on a phosphine complex of a transition metal.

12. A process according to Claim 11 where the transition metal is ruthenium.

13. A process according to Claim 11 where the transition metal is rhodium.

14. A process according to any of the above claims in which racemization is effected on the unwanted enantiomer at the same time as the resolution, so that essentially all the material is converted to the required isomer.

15. The olefin represented by formula 1



(1)

or an *N*-acyl or *N*-carbonyl derivative thereof.

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I[illegible]e undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) o[illegible]e Deregulation and Contracting Out Act 1994, to sign and issue certificates on behalf o[illegible]e Comptroller-General, hereby certify that annexed hereto is a true copy of the do[illegible]ents as originally filed in connection with the patent application identified therein.

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2. Patent application number *(The Patent Office will fill in this part)*	**9618836.2** 10 SEP 1996
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Chiroscience Limited Cambridge Science Park Milton Road Cambridge CB4 4WE United Kingdom
Patents ADP number *(if you know it)*	6534684001
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4. Title of the invention	RESOLUTION/RACEMISATION PROCESS
5. Name of your agent *(if you have one)*	GILL JENNINGS & EVERY
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Broadgate House 7 Eldon Street London EC2M 7LH
Patents ADP number *(if you know it)*	745002

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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

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Claim(s)	1
Abstract	
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Any other documents *(please specify)*	

11. For the Applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date
10 September 1996

12. Name and daytime telephone number of person to contact in the United Kingdom

PERRY, Robert Edward
0171 377 1377

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RESOLUTION/RACEMIZATION PROCESS

Field of the Invention

This invention relates to an economic process for the manufacture of a single isomer of methylphenidate through combining resolution with recycling of the undesired enantiomer.

Background to the Invention

Methylphenidate was first prepared as a mixture of the *erythro* [*R***S**] and *threo* [*R***R**] racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereoisomer.

The resolution of *threo* methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, a process first reported by Patrick *et al*, The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987). A more efficient resolution with *O,O*'-diaroyltartaric acids is disclosed in British Patent Application No. 9601228.1 and in US Application Serial No. 60/013,779, filed March 21, 1996, the contents of which are incorporated by reference; in particular, using *O,O*'-di-*p*-toluoyltartaric acids allows the diastereoisomeric salts to be very readily separated. In general, it is the d-*threo* [or (*R,R*)] enantiomer that is considered to have the preferred therapeutic activity.

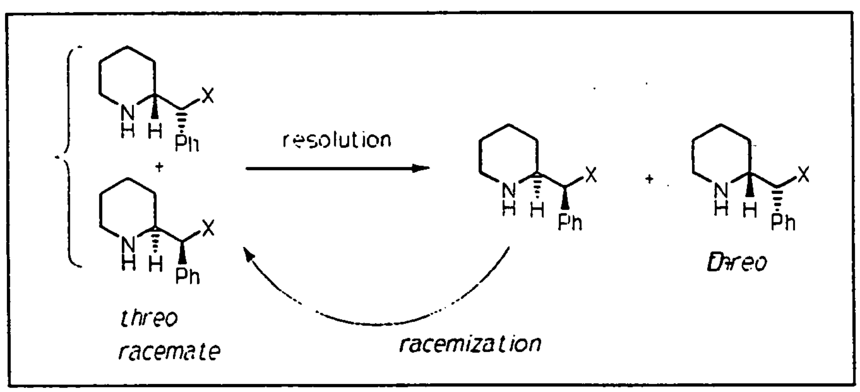
In an alternative approach disclosed in US-A-2957880, the amide of *erythro* methylphenidate (i.e. as $-CONH_2$ instead of $-CO_2Me$) is resolved with tartaric acid. Then amide hydrolysis, and equilibration at the benzylic centre, gives the *threo* isomer of the carboxylic acid which is esterified.

In order to establish an economic resolution process, it is highly desirable to be able to recycle the unwanted enantiomer into the resolution by way of a racemization. This becomes especially important when the resolution is performed late in a synthesis. An example of such a resolution and racemization procedure is in the case of naproxen where the single stereogenic carbon centre, which is benzylic and further activated by the carboxylate, is readily racemized. However, in the case of methylphenidate, there are two stereogenic centres. While one centre is similarly benzylic and can be epimerized as indicated in US-A-2957880, that converts the material into a mixture of diastereoisomers and not into the racemate that is required

for recycling. There is no method reported by which epimerization of the stereogenic centre adjacent to the piperidine nitrogen atom in methylphenidate can be effected.

Summary of the Invention

This invention is based on the novel discovery of methods to effect epimerization of *both* chiral centres in methylphenidate. Such epimerization gives a mixture of isomers in which equilibrium may favour the *threo* isomer; the result is that undesired enantiomer is converted predominantly into the racemate of the *threo* isomer which can then be reintroduced into the resolution. The overall process of a combination of resolution and racemization that may allow complete conversion into the required isomer is outlined in Scheme 1. The minor amount of *erythro* isomer that may remain after the racemization can be separated by conventional methods such as crystallization at this stage and subjected further to the epimerization conditions defined below. Alternatively, it can be recycled after passage through resolution of the *threo* isomer.

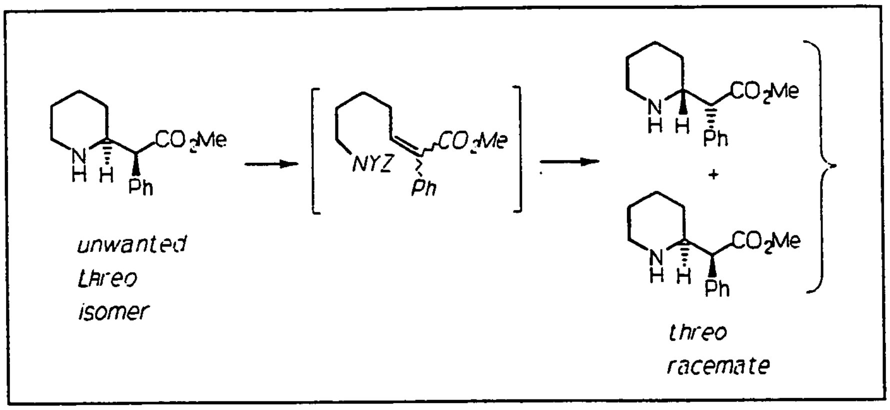


Scheme 1

In Scheme 1, the group X may be the $-CO_2Me$ function of methylphenidate and resolution carried out by known procedures, e.g. by formation of a diastereoisomeric salt with a chiral acid. Alternatively, the group X may be another resolvable function, e.g. a different ester, an amide, or a nitrile which can be converted into the methyl ester for methylphenidate. The resolution may be a

biotransformation that modifies the group X in one enantiomer so that the enantiomers are then separated.

The invention is the racemization which requires epimerization at both stereogenic centres. It has been discovered that such racemization can be carried out by way of activation at the piperidine nitrogen, to promote a fragmentation of the ring. The resultant olefinic intermediate has no chirality and recloses to a racemic mixture. Without wishing to be bound by theory, a possible mechanism is shown in Scheme 2 for the case of methylphenidate itself.



Scheme 2

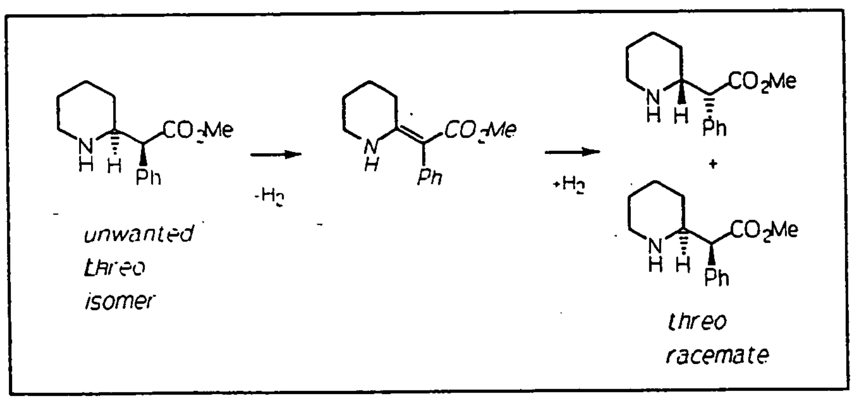
Description of the Invention

There are various ways in which the nitrogen may be activated, to promote the elimination-addition mechanism. One approach is treatment with an acid, for example a carboxylic acid, at a sufficiently high temperature, such as heating with propionic acid under reflux. This reaction is suitably conducted in an inert solvent such as toluene. The racemization can optionally be accelerated by the judicious addition of amounts of additives such as water or inorganic salts that will favour the charge separation in the transition state of the elimination.

In another method, treatment with an aldehyde or ketone (e.g. butyraldehyde or 2-cyclohexen-1-one) forms an iminium ion which, as well as activating the elimination, can render the proton at the piperidine stereogenic centre sufficiently

acidic to be removed by a base present. Thus a typical procedure involves heating the unwanted enantiomer with an aldehyde and a base in an appropriate solvent.

An alternative strategy for effecting racemization of the undesired isomer is by a dehydrogenation/hydrogenation sequence as depicted by Scheme 3. Thus, for example, the dehydrogenation may be by way of bromination at the benzylic position, followed by dehydrobromination to the olefin; this novel olefin is then hydrogenated. In this sequence, it is likely that the geometric isomer of the olefin indicated in Scheme 3 will be formed in preference because of the stabilisation provided by having the nitrogen and ester functions in a *trans* relationship. In that event, the usual *cis* hydrogenation will give the required *threo* diastereoisomer of methylphenidate. In a catalytic procedure, a catalyst is chosen that will remove and then reattach hydrogen. For example, a heterogeneous catalyst such as a transition metal adsorbed on carbon or a homogeneous catalyst such as a phosphine complex of ruthenium or rhodium may be used.



Scheme 3

The following Example illustrates the invention.

Example

Propionic acid (2 ml) was added to a solution of *d-threo* methylphenidate (5 g) in toluene (25 ml) and the solution was heated under reflux for 4 hours. The mixture was then cooled to ambient temperature and was rinsed with dilute sodium carbonate and then with water. The organic phase was separated and dried with magnesium sulphate and evaporated under reduced pressure. The resulting oil (4.3

g) was analysed by chiral HPLC which indicated the presence of all 4 stereoisomers of methylphenidate in roughly equal proportions.

CLAIMS

1. A process for obtaining a single enantiomer of methylphenidate, which combines resolution with racemization of the unwanted enantiomer.

2. A process according to claim 1, wherein the single enantiomer obtained is the d-*threo* isomer, i.e. the isomer of (*R*,*R*) absolute configuration.

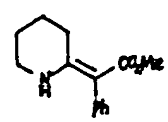
3. A process according to claim 1 or claim 2, wherein the racemization comprises heating the unwanted enantiomer with a carboxylic acid.

4. A process according to claim 1 or claim 2, wherein the racemization comprises the addition, to the unwanted enantiomer, of an aldehyde or ketone.

5. A process according to claim 1 or claim 2, wherein the racemization comprises dehydrogenation of the unwanted enantiomer, then hydrogenation of the resultant olefin.

6. A process according to claim 5, wherein the dehydrogenation comprises halogenation then dehydrohalogenation.

7. The olefin represented by formula 1



(1)

or an *N*-acyl or *N*-carbonyl derivative thereof.

APPENDIX C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Celia C Chang
Art Unit	:	1625
Applicants	:	Marianne Langston, Hooshang Shahriari Zavareh
Serial No.	:	09/928,139
Filed	:	October 8, 2001
For	:	The Manufacture of Single Isomer Methylphenidate

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF DR. HOOSHANG S. ZAVAREH UNDER 37 CFR ' 1.132

Sir:

I, Hooshang S. Zavareh, Ph.D., c/o Amedis Pharmaceuticals Ltd., 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GP, United Kingdom (formerly of Celltech R&D Ltd., Granta Park, Great Abington, Cambridge CB1 6GS, United Kingdom), hereby declare:

THAT, I am a co-inventor of the subject matter claimed in this Application;

THAT, I have read and understood the specification and claims of this Application;

AND, being thus duly qualified, do further declare:

Methylphenidate has two chiral centres in the same molecule. It is relatively easy to racemise the molecule at one such centre. In order to racemise one of the enantiomers so that all four are obtained, racemisation must occur at both centres. This involves abstraction of a proton. It is therefore surprising that an acid causes this racemisation to occur.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: H S Zavareh
Dr. Hooshang S. Zavareh

Date: 15 July 2003

APPENDIX D

Approaches to the Preparation of Enantiomerically Pure (2*R*,2'*R*)-(+)-*threo*-Methylphenidate Hydrochloride

Mahavir Prashad

Process Research and Development, Chemical and Analytical Development, Novartis Institute for Biomedical Research, 59 Route 10, East Hanover, New Jersey 07936, USA
Fax (+1) 973-781-2188, e-mail mahavir.prashad@pharma.Novartis.com

Received March 13, 2001; Accepted April 20, 2001

Abstract: Various approaches to the preparation of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) are reviewed. These approaches include synthesis using enantiomerically pure precursors obtained by resolution, classical and enzyme-based resolution approaches, enantioselective synthesis approaches, and approaches based on enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate followed by epimerization at the 2-position.

Keywords: attention deficit hyperactivity disorder; enantioselective synthesis; enzymatic hydrolysis; (2*R*,2'*R*)-*threo*-methylphenidate; resolution; ritalin

1 Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed behavioral disorder in children. ADHD persists across the full span of development, from preschool to school age and adolescence, and frequently continues into adult life.[1] The diagnosis of ADHD is a clinical rather than a specific medical diagnosis. To date there are no laboratory tests that can be used to make a definitive diagnosis of ADHD.[2,3] Racemic (±)-*threo*-methylphenidate hydrochloride [Ritalin® hydrochloride, methyl phenyl-(2-piperidyl)acetate] is a mild nervous system stimulant and is currently the most widely used drug for the treatment of children with ADHD.[4,5] The psychostimulant properties of (±)-*threo*-methylphenidate have been linked to its binding to a site on the dopamine receptor, resulting in inhibition of dopamine re-uptake and enhanced levels of synaptic dopamine. This stimulation is believed to regulate attention and impulsivity of ADHD in children. Racemic (±)-*threo*-methylphenidate, however, possesses side effects, e.g., anorexia, insomnia, weight loss, dizziness, dysphoria, and has potential for substance abuse in patients, especially when administered intravenously or through inhalation as it produces an euphoric effect. It has been postulated that the euphoric effect of (±)-*threo*-methylphenidate is primarily due to the action of L- or (2*S*,2'*S*)-(−)-*threo*-enantiomer. Enhanced relief for patients with ADHD was recently documented[6] with newly formulated D- or (2*R*,2'*R*)-(+)-*threo*-methylphenidate (Figure 1), while reducing side effects and euphoric effects. Additionally, it has been shown that (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) is more potent in the induction of locomotor activity and has a higher affinity for the dopamine transporter than the (2*S*,2'*S*)-(−)-*threo*-enantiomer 2.[7] A recent report has demonstrated that pharmacological specificity resides entirely in the (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) and that the binding of the (2*S*,2'*S*)-(−)-*threo*-enantiomer 2 in human brain is mostly non-specific.[8] This was further confirmed by positron-emission tomography (PET) images of human brain after administration of [^{11}C]-(2*R*,2'*R*)-(+)-*threo*-methylphenidate and [^{11}C]-(2*S*,2'*S*)-(−)-*threo*-methylphenidate, which showed that the [^{11}C]-(2*R*,2'*R*)-(+)-*threo*-enantiomer concentrated in basal ganglia, where it binds to the dopamine transporter.

Mahavir Prashad was born in Ghaziabad (U.P.), India. He received his B.Sc. and M.Sc. degrees from M. M. College, Modinagar (University of Meerut), India, and his Ph.D. from the Central Drug Research Institute, Lucknow, India. After a post-doctoral fellowship at Heriot-Watt University, Edinburgh and the University of Bath in the U.K., an Alexander von Humboldt fellowship at the Universität Bielefeld, Germany, and a post-doctoral fellowship at Duke University, Durham, North Carolina, he joined Novartis Pharmaceuticals Corporation (formerly Sandoz). He is presently a senior fellow and group leader in the Process R & D section of Chemical and Analytical Development at Novartis. His research interests include the development of efficient and practical synthetic methods and enantioselective synthesis.

The [^{11}C]-(2*S*,2'*S*)-(–)-*threo*-enantiomer did not bind, indicating that the (2*R*,2'*R*)-(+)-*threo*-enantiomer 1 is the active form.[9] Thus, to segregate the desired pharmacological activities from side effects, there is a great interest for preparing enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) on a large scale.

From the historical perspective, racemic methylphenidate was first synthesized (Scheme 1) in 1944 by Panizzon[10,11] and was originally marketed as a mixture of two racemates: 80% of (±)-*erythro* and 20% of (±)-*threo*. Subsequent studies led to the discovery that the central stimulant activity was associated with only one, i.e., the (±)-*threo* racemate[11–13] and that the (2*R*,2'*R*)-(+)-*threo*-enantiomer was 5[13] to 38[14] times more active than the (2*S*,2'*S*)-(–)-*threo*-enantiomer. The metabolic pathway for methylphenidate in dogs and rats has also been delineated.[15] While the development of efficient routes for the synthesis of racemic (±)-*threo*-methylphenidate and its analogues for structure-activity relationship studies remains a topic of interest,[16–19] this review focuses only on the approaches reported to date for the preparation of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1).

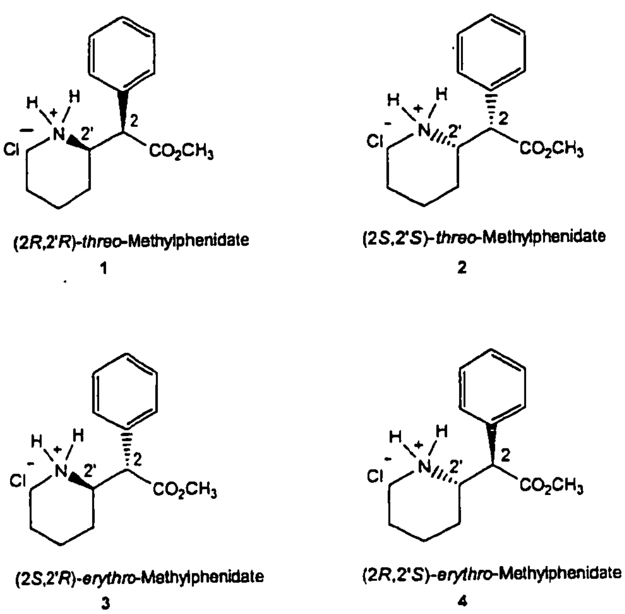


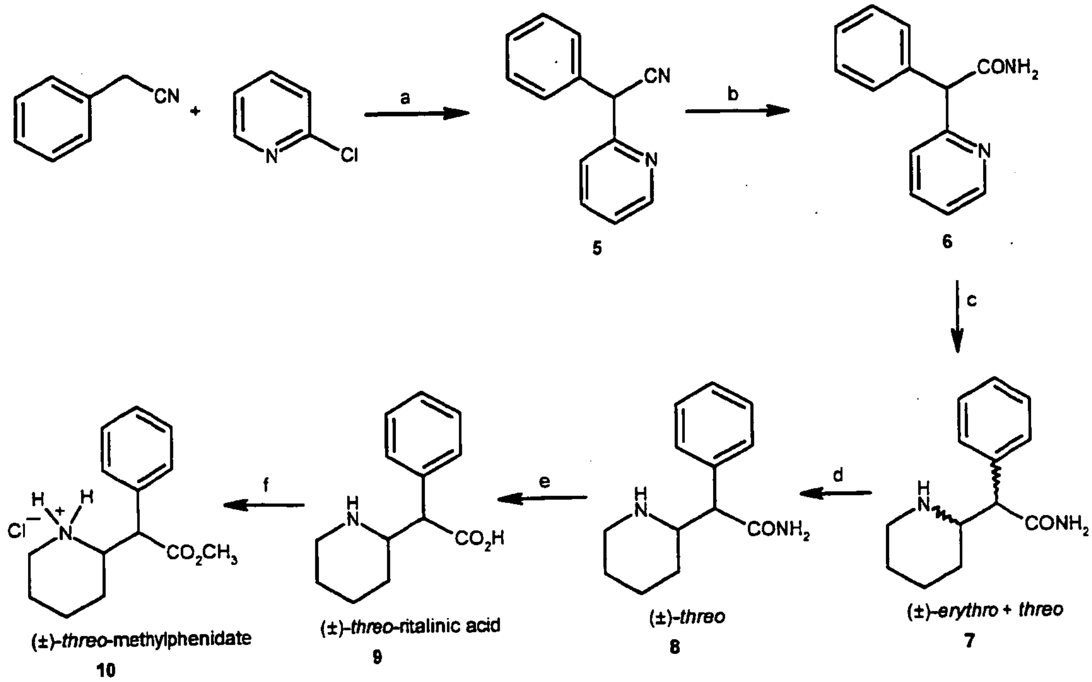
Figure 1.

2 Methods for the Enhancement of Enantiomeric Purity of Enriched 1

Enrichment of the enantiomeric purity of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) was first reported by Patrick et al. by crystallization from a mixture of methanol and ether.[7] We (Novartis) also recently reported that the enantiomeric purity of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride salt (1) was enhanced from 80% ee to >98% ee by recrystallization from a mixture of methanol and *t*-butyl methyl ether (1:1.7 v/v).[20] An enrichment of the enantiomeric purity of 1 from this solvent mixture was then reported by Faulconbridge et al.[21] Thus, any approach which yields enriched (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) would afford enantiomerically pure 1 after recrystallization from this solvent mixture, but at the cost of loss in yield.

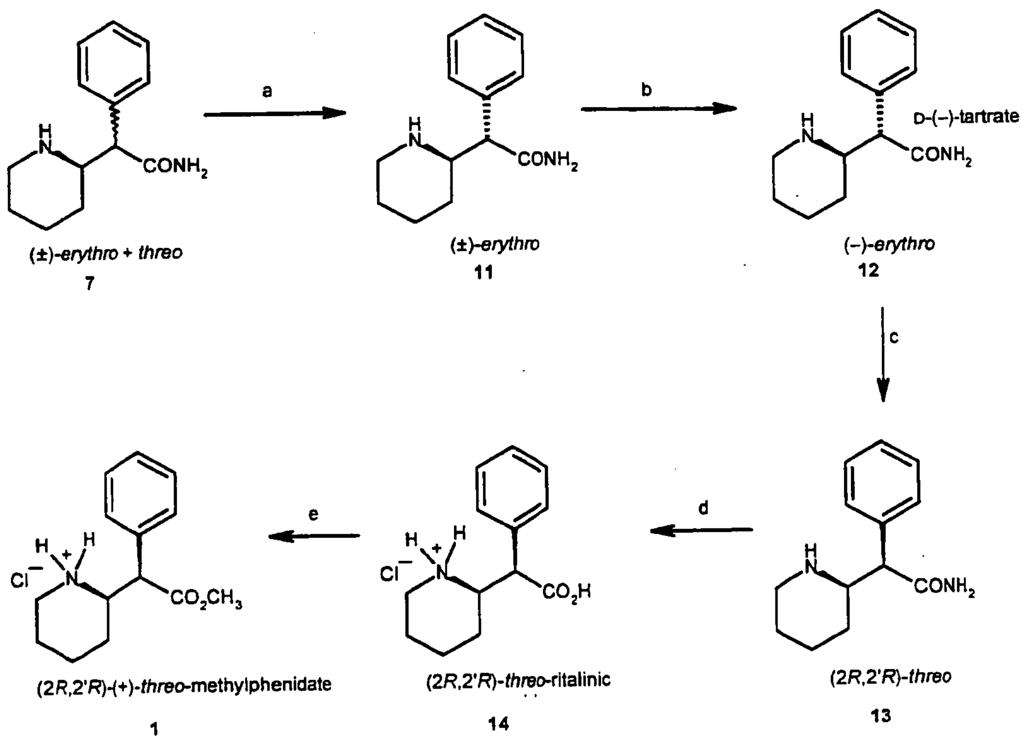
3 Approaches Using Enantiomerically Pure Precursors Obtained by Resolution

The first preparation (Scheme 2) of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) was reported by R. Rometsch of former Ciba Pharmaceuticals (now Novartis).[12,13] Enantiomerically pure L-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (12), obtained by the resolution of (±)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (11) with D-(–)-tartaric acid in 96% ethanol, was subjected to epimerization to the desired (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (13) with aqueous KOH. (2*R*,2'*R*)-*threo*-2-Phenyl-2-(2-piperidyl)acetamide (13), thus obtained, was converted to the desired (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) by hydrolysis and esterification. This approach has recently been further optimized by Ramaswamy and Kheta-



(a) NaOH; (b) H_2SO_4; (c) H_2, Pt, CH_3CO_2H; (d) KOH, H_2O; (e) H_2SO_4, H_2O (f) CH_3OH, HCl.

Scheme 1.

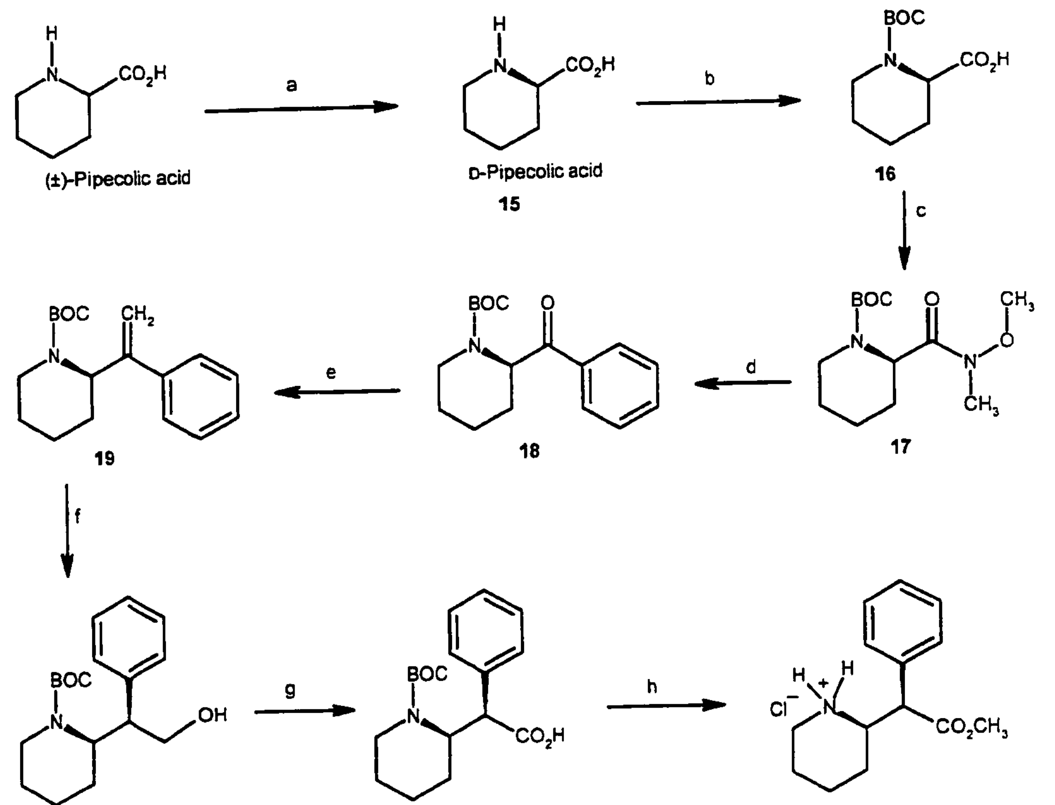


(a) C_2H_5OH, HCl gas; (b) D-(−)-tartaric acid, C_2H_5OH; (c) 50% KOH, reflux, recrystallization;
(d) 6 N HCl; (e) CH_3OH, HCl.
or
(b) D-(−)-tartaric acid, CH_3OH (40%); (c) *t*-BuOK, toluene, 70 °C (85%); (d) H_2SO_4; (e) CH_3OH, HCl (80%).

Scheme 2.

ni.[22,23] Resolution of (±)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (11) with D-(–)-tartaric acid in methanol also afforded a 40% yield of L-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (12). Epimerization of L-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (12) with potassium *tert*-butoxide in toluene at 70 °C furnished (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)-acetamide (13) in 85% yield, which was converted to the desired methyl ester (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) by treatment with concentrated sulfuric acid in refluxing methanol and HCl salt preparation in 80% yield.[22,23]

Another synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) using an enantiomerically pure starting material, D-pipecolic acid (15), was reported by Perel et al. (Scheme 3).[24] Enantiomerically pure D-pipecolic acid (15) was obtained in 37% yield by recrystallization of diastereomeric tartrate salt, followed by the separation of the desired amino acid from tartaric acid by ion-exchange chromatography. D-Pipecolic acid (15) was protected with a BOC group to afford *N*-BOC-D-pipecolic acid (16) in 97% yield. The key amino ketone (18; Scheme 3) was prepared from *N*-BOC-D-pipecolic acid (16) in two steps involving its conversion to the *N*-methoxy-*N*-methyl amide 17, followed by the reaction of amide 17 with phenyllithium. The amino ketone 18 underwent a Wittig olefination with methyltriphenylphosphonium bromide in the presence of potassium *tert*-butoxide to give the alkene 19 in high yield. The transformation of alkene 19 to the desired *threo* diastereomer of alcohol 20, via hydroboration/oxidation, was critical to introduce the second stereogenic center. The *threo* isomer was favored with non- and disubstituted boranes while the *erythro* alcohol was the major isomer in the presence of monosubstituted thexylborane. Only the *threo* isomer was isolated by hydroboration of alkene 19 with (+)-IPC-BH_2 in 55% yield. Hydroboration with BH_3·THF gave a 72:28 mixture of *threo* and *erythro* isomers, respectively, from which the *threo* alcohol 20 was isolated in the highest yield (64%) after chromatography. Oxidation of *threo* alcohol 20 with PDC in DMF followed by esterification of the resulting acid 21 with diazomethane, and *N*-BOC group deprotection with 3 N methanolic HCl furn-



(a) (i) L-tartaric acid (ii) recrystallizaton (iii) ion-exchange chromat. (37%); (b) $(BOC)_2O$, $(C_2H_5)_3N$ (97%); (c) BOP, $(C_2H_5)_3N$, CH_3NHOCH_3.HCl (93%); (d) PhLi (47%); (e) CH_3PPh_3Br, *t*-BuOK (93%); (f) BH_3·THF, NaOH, H_2O_2 (64%); (g) PDC, DMF (100%); (h) (i) CH_2N_2 (ii) HCl (67%).

Scheme 3.

ished (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 67% yield after recrystallization from ethanol/ether.

4 Classical Resolution Approaches

A resolution process is more attractive and economical if the undesired enantiomer can be recycled via racemization. However, in the case of methylphenidate, such a racemization is challenging because there are two stereogenic centers which have to be epimerized. A method to affect the racemization at both stereogenic centers has been demonstrated by refluxing a solution of (2*R*,2'*R*)-*threo*-methylphenidate (1) with propionic acid in toluene to afford a mixture of four stereoisomers in roughly equal proportions.[26] Although the exact mechanism has not been ascertained, it probably involves the opening of the ring via protonation of the piperidine nitrogen. The putative olefinic intermediate has no chirality and recloses to a racemic mixture. These results suggested that the recycling of the undesired enantiomer is possible.

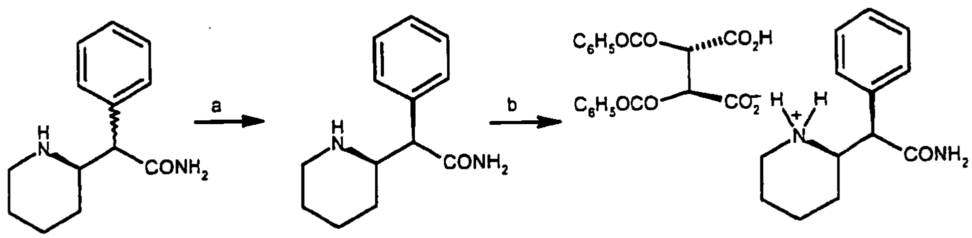
4.1 Resolution of Amide and Acid Derivatives of 1

Resolution of (±)-*threo*-ritalinic acid hydrochloride salt with (*S*)-(−)-α-methylbenzylamine in a mixture of ethanol and water (95:5 v/v) gave the diastereomeric salt enriched with (2*R*,2'*R*)-*threo*-ritalinic acid with 77% ee.[27] Ritalinic acid itself did not undergo any effective degree of resolution with any of a wide range of resolving agents. A novel double salt may have been formed from (±)-*threo*-ritalinic acid hydrochloride as a hydrate. Esterification and enrichment of the resulting enriched (2*R*,2'*R*)-*threo*-methylphenidate hydrochloride with methanol and *tert*-butyl methyl ether would furnish 1 in high enantiomeric purity.

Resolution of (±)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (8; Scheme 4), obtained by epimerization of a mixture of (±)-*erythro*- and (±)-*threo*-2-phenyl-2-(2-piperidyl)acetamides with potassium *tert*-butoxide in toluene at 70 °C, with dibenzoyl-D-tartaric acid (D-DBTA) in 2-propanol to afford (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)acetamide dibenzoyl-D-tartrate salt (22) in 40% yield has also been achieved.[25] The diastereomeric salt 22 would furnish enantiomerically pure 1 after hydrolysis and esterification.

4.2 Resolution of (±)-*threo*-Methylphenidate (10)

Since racemic (±)-*threo*-methylphenidate hydrochloride (10) is readily available, its resolution would provide a practical method for the preparation of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1). The resolution of (±)-*threo*-methylphenidate (10) was first reported by Patrick et al. in 1987 using (*R*)-(−)-binaphthyl-2,2'-diyl hydrogen phosphate (BNDHP) as the resolving agent (Scheme 5).[7] The (±)-*threo*-methylphenidate hydrochloride (10) was first converted to the free base by treatment with aqueous sodium carbonate and extracted with ether. Removal of ether furnished the (±)-*threo*-methylphenidate (10) free base. Resolution of the free base with BNDHP in a warm mixture of acetone and methanol (95:5) followed by cooling to 5 °C gave the diastereomeric BNDHP salt 23 in 45% yield which was enriched with (2*R*,2'*R*)-(+)-*threo*-methylphenidate. The enantiomeric purity of this salt 23, as determined by GC, was 85–90%. A further recrystallization of this crude salt with a mixture of acetone and methanol (98:2) increased the enantiomeric purity to 95 to 97%. Conversion of this diastereomeric BNDHP salt to the free base and HCl salt formation with ethereal HCl gave the crude (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride salt (1). A recrystallization of this HCl salt from methanol and ether furnished 1 in 99% enantiomeric purity. However, this method was found to be non-reproducible and furnished 1 with only 92.6% ee (2*R*,2'*R*:2*S*,2'*S* = 96.3:3.7).[28] Both of these reports lacked critical experimental details, in particular the volume of the sol-



(±)-*erythro* + *threo*
7

(±)-*threo*
8

(2*R*,2'*R*)-*threo*
22

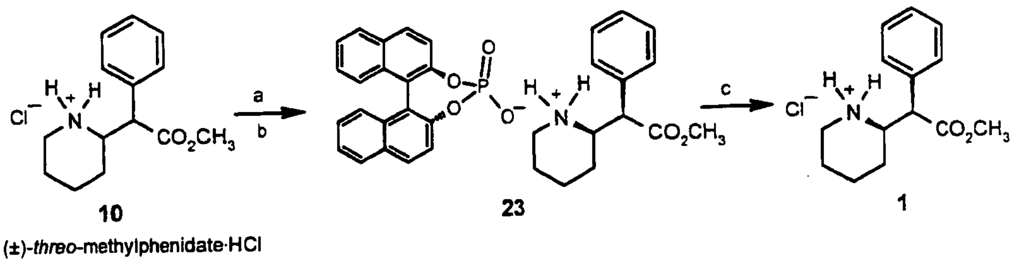
(a) *t*-BuOK, toluene, 70 °C; (b) dibenzoyl-D-(−)-tartaric acid, 2-propanol (40%).

Scheme 4.

vent used in the resolution and recrystallization steps. Subsequently, we (Novartis) reported that the resolution of (±)-*threo*-methylphenidate free base with BNDHP under the literature conditions (except unknown solvent volume) gave a diastereomeric salt with poor enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 62.8:37.2). After a detailed investigation, we (Novartis) discovered that the resolution of (±)-*threo*-methylphenidate free base in acetone–methanol mixture (98:2) with 0.5 equivalents of BNDHP, instead of 1.0 equivalent, gave the diastereomeric salt in 31% yield with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 100:0).[29,30] These results demonstrated a rare example where the use of 0.5 equivalents of the resolving agent gave excellent resolution compared to 1.0 equivalent of the same resolving agent. A practical process for the resolution of (±)-*threo*-methylphenidate free base with 0.5 equivalents of BNDHP in a mixture of isopropyl acetate and methanol (85:15 v/v) was developed by us to afford the diastereomeric BNDHP salt (23; Scheme 5) of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 36% yield with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.2:0.8).[29,30] No extra recrystallizations were necessary to enhance the enantiomeric purity of the diastereomeric BNDHP salt. This diastereomeric salt was then converted to enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) by free base generation and HCl salt formation in an overall yield of 31.4% with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.9:0.1). To avoid a step for free-base generation, a direct resolution of the (±)-*threo*-methylphenidate hydrochloride salt (10) with BNDHP in the presence of 4-methylmorpholine, which generates the free base *in situ*, in a mixture of methanol and water (1.6:1 v/v), was also reported to afford the (2*R*,2'*R*)-(+)-*threo*-methylphenidate BNDHP salt with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.1:0.9) and in 27% yield.

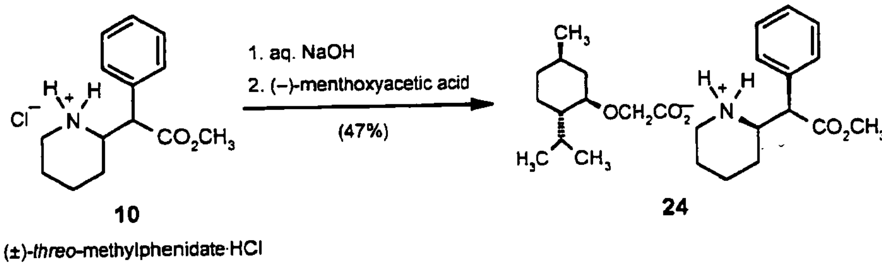
Recently, resolution of (±)-*threo*-methylphenidate (10) free base with (–)-menthoxyacetic acid in 2-propanol was reported by Zavareh (Scheme 6) to afford (–)-menthoxyacetate salt 24 of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 47% yield and 98% ee.[31]

Because both (*R*)-(–)-binaphthyl-2,2'-diyl hydrogen phosphate (BNDHP) and (–)-menthoxyacetic acid are relatively expensive, the search for a less-expensive resolving agent continued. Harris et al. reported the

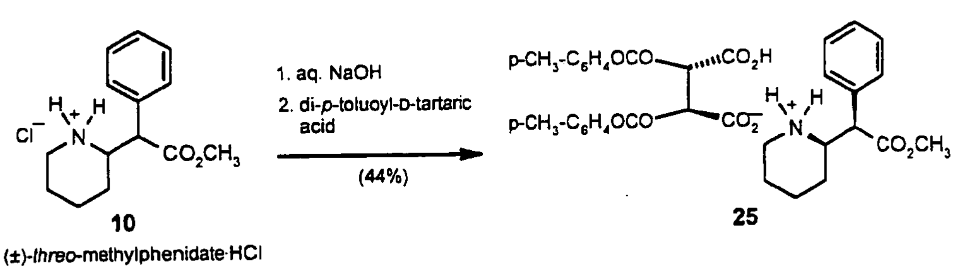


(a) aq. NaOH; (b) (*R*)-(–)-binaphthyl-2,2'-diyl hydrogen phosphate (36%);
(c) (i) aq. NaOH, *i*-PrOAc (ii) conc. HCl (iii) water–conc. HCl (recrystallization).

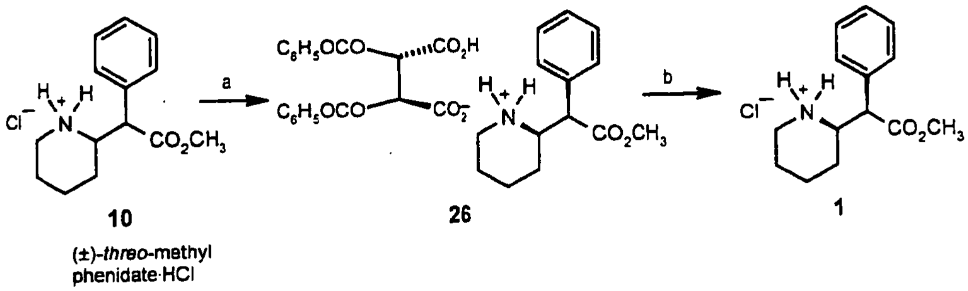
Scheme 5.



Scheme 6.



Scheme 7.



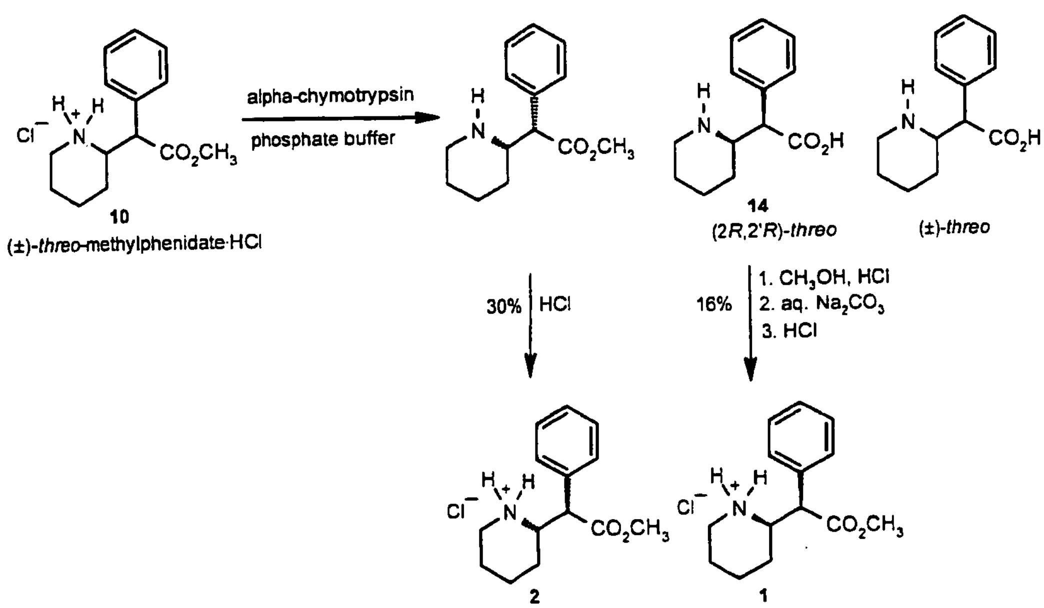
(a) dibenzoyl-D-(−)-tartaric acid, 4-methylmorpholine, CH_3OH–water (44%); (b) (i) aq. NaOH, *i*-PrOAc (ii) conc. HCl (iii) water–conc. HCl (recrystallization).

Scheme 8.

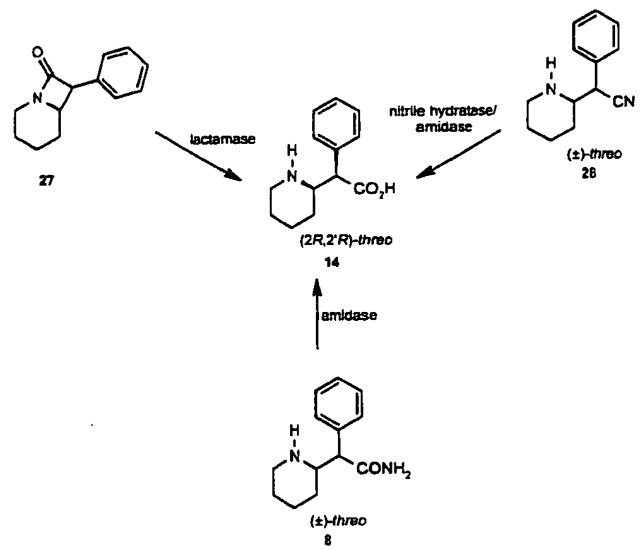
resolution of (±)-*threo*-methylphenidate (**10**) free base, generated from the HCl salt by base treatment, with the cheaper *O,O'*-di-*p*-toluoyl-D-tartaric acid in acetone containing 2% of methanol (Scheme 7).[28] It afforded the *O,O'*-di-*p*-toluoyl-D-tartrate (D-DPTTA) salt **25** of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 44.3% yield and 97% ee. The enantiomeric purity of this salt was further enhanced to >99% ee and in 92% recovery by reslurrying it in acetone containing 2% of methanol. We (Novartis) also reported an efficient and large scale resolution of the (±)-*threo*-methylphenidate hydrochloride salt with the much cheaper *O,O'*-dibenzoyl-D-tartaric acid (Scheme 8).[32,33] An advantage of these new conditions was that the (±)-*threo*-methylphenidate hydrochloride salt (**10**) was used directly for the resolution, thus avoiding the necessity for the generation of the free base. Thus, a direct resolution of (±)-*threo*-methylphenidate hydrochloride salt (**10**) with 1.0 equivalent of *O,O'*-dibenzoyl-D-tartaric acid in the presence of 1.0 equivalent of 4-methylmorpholine in a mixture of methanol and water (2:1 v/v) afforded *O,O'*-dibenzoyl-D-tartrate (D-DBTA) salt **26** of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 38% yield with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.54:0.46). The yield was further increased to 44%, without any loss of enantiomeric purity, by cooling the mixture to 0 °C. The *O,O'*-dibenzoyl-D-tartrate salt of (2*R*,2'*R*)-(+)-*threo*-methylphenidate was then converted to (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**) in 40% overall yield (from **10**) with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = >99.9:<0.1).

5 Enzyme-Based Resolution Approaches

The resolution of (±)-*threo*-methylphenidate (**10**) free base by enantioselective enzymatic hydrolysis was first reported by us (Novartis) (Scheme 9).[20] α-Chymotrypsin and subtilisin carlsberg exhibited selectivity towards the hydrolysis of the (2*R*,2'*R*)-enantiomer.

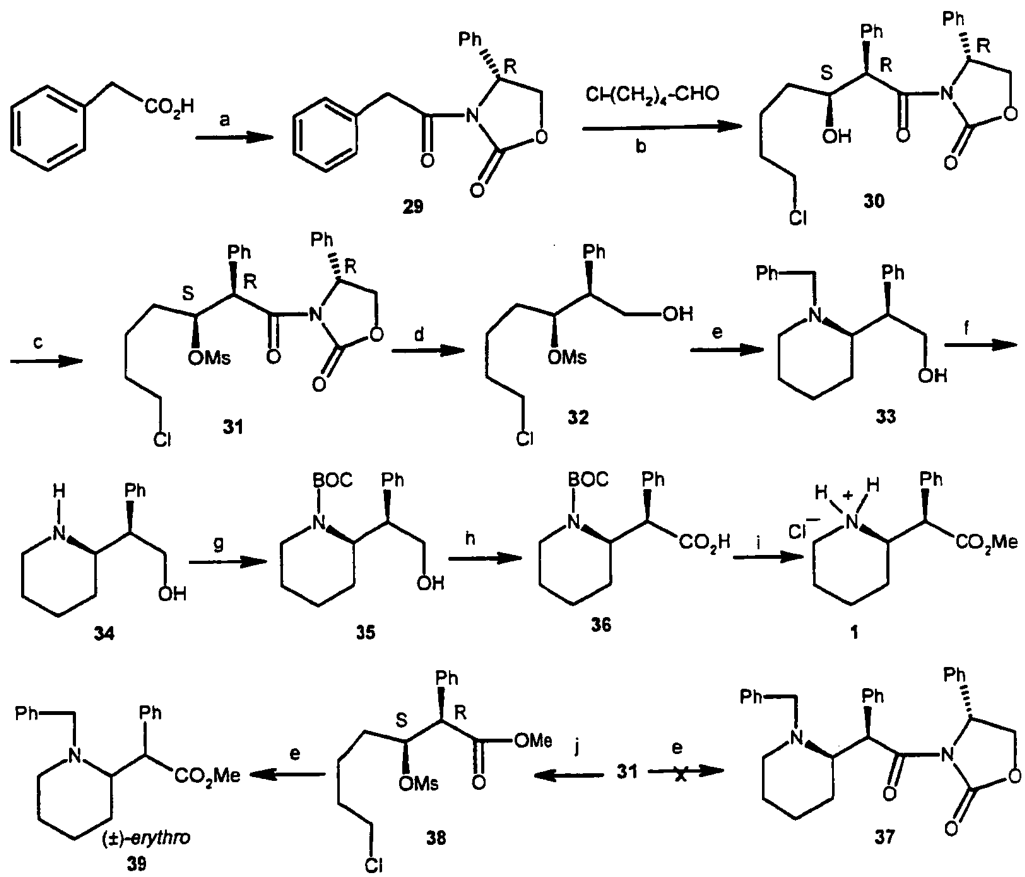


Scheme 9.



Scheme 10.

Hydrolysis of (±)-*threo*-methylphenidate (**10**) free base with α-chymotrypsin in pH 7.0 phosphate buffer furnished a heterogeneous mixture from which enantiomerically pure (2*S*,2'*S*)-(–)-*threo*-methylphenidate hydrochloride (**2**) was isolated in 30% yield with >99% ee after extractive work-up and conversion of the free base to the HCl salt. The solid, which precipitated during the enzymatic hydrolysis in 30% yield, was identified as racemic (±)-*threo*-ritalinic acid. It was formed as a result of the hydrolysis of some of the (2*S*,2'*S*)-enantiomer. The (2*R*,2'*R*)-*threo*-ritalinic acid (**14**) was highly soluble in the aqueous medium and did not precipitate. It was isolated from the aqueous layer by lyophilization, esterification with methanol, and basic work-up to afford (2*R*,2'*R*)-(+)-*threo*-methylphenidate (**1**) free base in 80% ee. Treatment of this free base with HCl gas followed by recrystallization of the resulting HCl salt from a mixture of methanol and *t*-butyl methyl ether (1:1.7 v/v) afforded (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydro-



(a) (*R*)-4-phenyl-2-oxazolidinone, pivaloyl chloride, Et_3N, toluene (78%); (b) i) *n*-Bu_2BOTf, DIEA, CH_2Cl_2 or toluene, –20 °C to RT, ii) 30% H_2O_2, MeOH (78%); (c) Ms_2O, C_5H_5N, 0 °C or MsCl, Et_3N (92%); (d) $NaBH_4$, THF–H_2O, 0 °C to RT (91%); (e) $PhCH_2NH_2$ (10 eq.), 85 °C, 3 h (60%); (f) H_2, 10% Pd-C, EtOH (92%); (g) $(BOC)_2O$, THF (82%); (h) $NaIO_4$, $RuCl_3 \cdot H_2O$, CH_3CN, H_2O, CCl_4 (80%); (i) MeOH, HCl, 50 °C, overnight (70%); (j) MeOLi, MeOH, 0 °C (50%).

Scheme 11.

chloride (1) in 16% yield and >98% ee. Thus, the differences in the solubilities of the (±)- and (2*R*,2'*R*)-*threo*-ritalinic acids in the aqueous medium led to selective crystallization of the former during enzymatic hydrolysis and made their separation possible. Similar results were obtained using subtilisin carlsberg as the enzyme yielding (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 15% yield with >98% ee, and (2*S*,2'*S*)-(–)-*threo*-methylphenidate hydrochloride (2) in 26% yield with >99% ee.

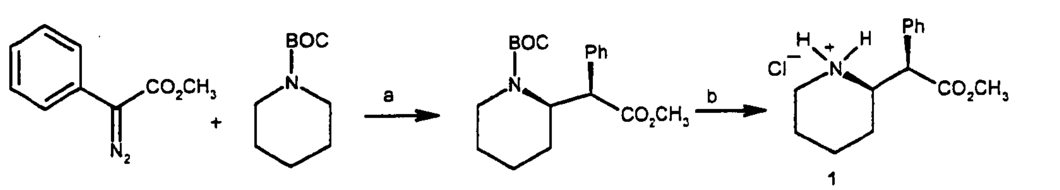
Enzymatic hydrolysis of (±)-*threo*-methylphenidate (10) free base with an esterase/lipase enzyme, obtained from various microorganisms, was also reported by Zeitlin et al.[34] to furnish (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 96% ee. (±)-*trans*-7-Phenyl-1-azabicyclo[4.2.0]octan-8-one (27) was also hydrolyzed using a lactamase enzyme in pH 7 phosphate buffer (Scheme 10) to afford (2*R*,2'*R*)-*threo*-ritalinic acid (14) with >96% ee. (2*R*,2'*R*)-*threo*-Ritalinic acid (14) was also obtained by hydrolysis of (±)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (8) with amidase or (±)-*threo*-2-phenyl-2-(2-piperidyl)acetonitrile (28) using a nitrile hydratase and amidase enzymes in 98% ee.[34] (2*R*,2'*R*)-*threo*-Ritalinic acid would furnish (2*R*,2'*R*)-*threo*-methylphenidate hydrochloride 1 after esterification and HCl salt formation.

6 Enantioselective Synthesis Approaches

We (Novartis) reported the first enantioselective synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1), which involved an asymmetric aldol condensation of 5-chlorovaleraldehyde with the (*Z*)-boron enolate derived from *N*-phenylacetyl-(*R*)-4-phenyl-2-oxazolidinone (29) as the key step to generate both stereogenic centers of 1 with desired absolute configuration (Scheme 11).[35]

Reaction of 5-chlorovaleraldehyde with the (*Z*)-boron enolate derived from *N*-phenylacetyl-(*R*)-4-phenyl-2-oxazolidinone (29) afforded the desired single diastereomer 30, as confirmed by ^{1}H NMR, in 78% yield. Mesylation of 30 with either methanesulfonic anhydride and pyridine in dichloromethane or methanesulfonyl chloride and triethylamine in toluene yielded the mesylate 31 in 92% yield. Attempts to construct the piperidine ring by the cyclization of 31 to 37 by treatment with benzylamine at 85 °C gave a complicated mixture. It was postulated that the undesired ring opening of the 2-oxazolidinone by benzylamine and the steric bulk of this chiral auxiliary may be responsible for this unexpected outcome. Alternatively, the methyl ester 38 underwent cyclization with benzylamine, however, the product was characterized to be (±)-*erythro*-methylphenidate 39. These results could be explained based on the elimination of the mesylate, which destroyed both stereogenic centers to furnish the α,β-unsaturated ester intermediate, which then underwent a Michael addition with benzylamine, followed by cyclization. To circumvent this problem, the methyl ester group was replaced with the corresponding alcohol function prior to the cyclization, which could be oxidized back to the desired carboxylic ester functionality afterwards. Reductive removal of the chiral auxiliary in 31 with sodium borohydride in THF and water yielded the desired alcohol 32 in 91% yield. Treatment of alcohol 32 with benzylamine at 85 °C afforded the desired piperidine intermediate 33 in 60% yield. Hydrogenation of 33 with 10% Pd-C in ethanol furnished the amino alcohol 34 in 92% yield, which was acylated with di-*tert*-butyl dicarbonate to afford the *N*-BOC-protected alcohol 35 in 82% yield. Oxidation of alcohol 35 with $NaIO_4$ and $RuCl_3$ furnished the acid 36 in 80% yield. Treatment of acid 36 with methanol in the presence of HCl gas at 50 °C gave the desired (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 70% yield. The enantiomeric purity of 1 was >99% ee and the overall yield from phenylacetic acid was 13% after 9 steps.

Winkler et al. reported[36–37] an enantioselective synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) based on the rhodium-mediated C–H insertion of methyl phenyldiazoacetate (40) with *N*-BOC-piperidine (41). Thus, reaction of methyl phenyldiazoacetate (40) with *N*-BOC-piperidine (41;



(a) Rh_2(5*R*-MEPY)$_4$, cyclohexane, 50 °C; (b) HCl, CH_3OH
or
(a) Rh_2(*S*-biDOSP)$_2$, 2,3-dimethoxybutane, RT; (b) TFA

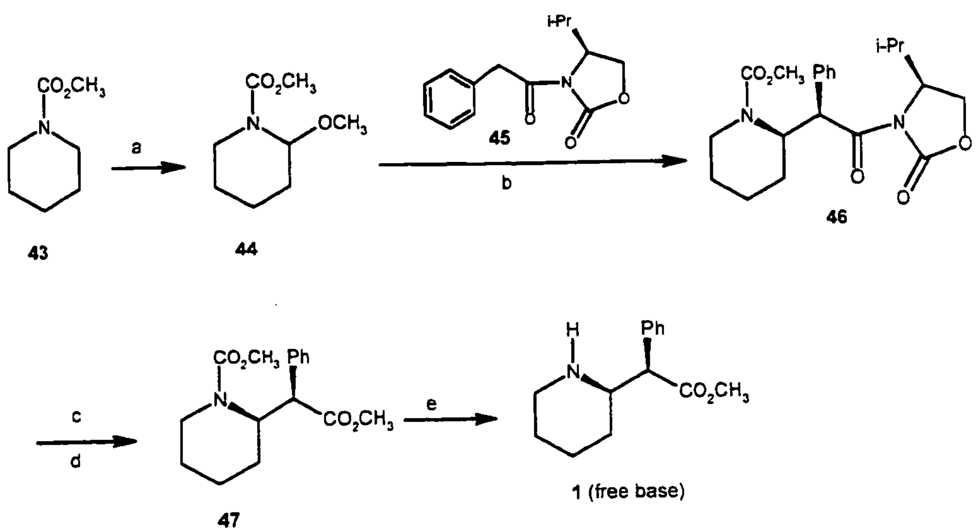
Scheme 12.

Scheme 12) in cyclohexane at 50 °C in the presence of 1 mol % of $Rh_2(5R\text{-MEPY})_4$ led to the selective formation of *N*-BOC-D-*threo*-methylphenidate (42) in 64.5% yield. Deprotection of 42 with HCl gas in methanol furnished crude (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 68.5% yield with 94% de and 69% ee. Two recrystallizations of this crude product from a mixture of ethanol and diethyl ether (1:1 v/v) gave 1 in 26% yield with 95% de and >95% ee.

Independently, Davies et al.[58] also reported the same approach as described above by Winkler et al. The $Rh_2(S\text{-DOSP})_4$-catalyzed decomposition of methyl phenyldiazoacetate (40) in the presence of *N*-BOC-piperidine (41, 4 equivalents) in 2,3-dimethylbutane at room temperature, followed by treatment with trifluoroacetic acid, resulted in the formation of a mixture of *threo*- and *erythro*-methylphenidate in 49% yield. However, the *threo*-isomer was the minor diastereomer and was formed in only 34% ee. A major improvement in enantioselectivity and diastereoselectivity was achieved by carrying out the reaction with the $Rh_2(S\text{-biDOSP})_2$ catalyst. The ratio of *threo* to *erythro* isomers was improved to 2.5:1 (73% yield), respectively. The (2*R*,2'*R*)-*threo*-isomer was formed in 86% ee and isolated in 52% yield.

Matsumura et.al.[39,40] described a convenient method for the preparation of (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) free base starting from the easily available *N*-methoxycarbonylpiperidine (43; Scheme 13) involving a highly stereoselective coupling reaction of the α-methoxylated carbamate 44 with the Evans imide 45 as the key step. An electrochemical α-methoxylation of 43 in methanol afforded the *N*-protected α-methoxypiperidine 44 in 85% yield. The C–C bond forming reaction between 44 and 45 was successfully achieved by using a combination of $TiCl_4$ and diisopropylethylamine (DIPEA) to give the coupled product 46 with high diastereo- and enantioselectivity. The configuration of 46 was determined at the stage of 47 and 1 by chiral stationary phase HPLC analysis. The ratio of *erythro*-47 to *threo*-47 was 5.3:94.7 and the ee of the *threo* isomer was 99.6%. The predominant formation of the (2*R*,2'*R*)-isomer formation suggested that the reaction might proceed through a coordinated intermediate in which the acyliminium ion generated from 44 approaches the thermodynamically stable *Z*-form of the titanium enolate generated from 45 from the *si* face. Treatment of the carbamate 46 with LiOH in the presence of H_2O_2, followed by the treatment of the resulting acid with CH_2N_2, furnished the methyl ester 47 in 54% yield. The deprotection at the *N*-methoxycarbonyl group with $(CH_3)_3SiI$ afforded (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) free base in 75% yield.

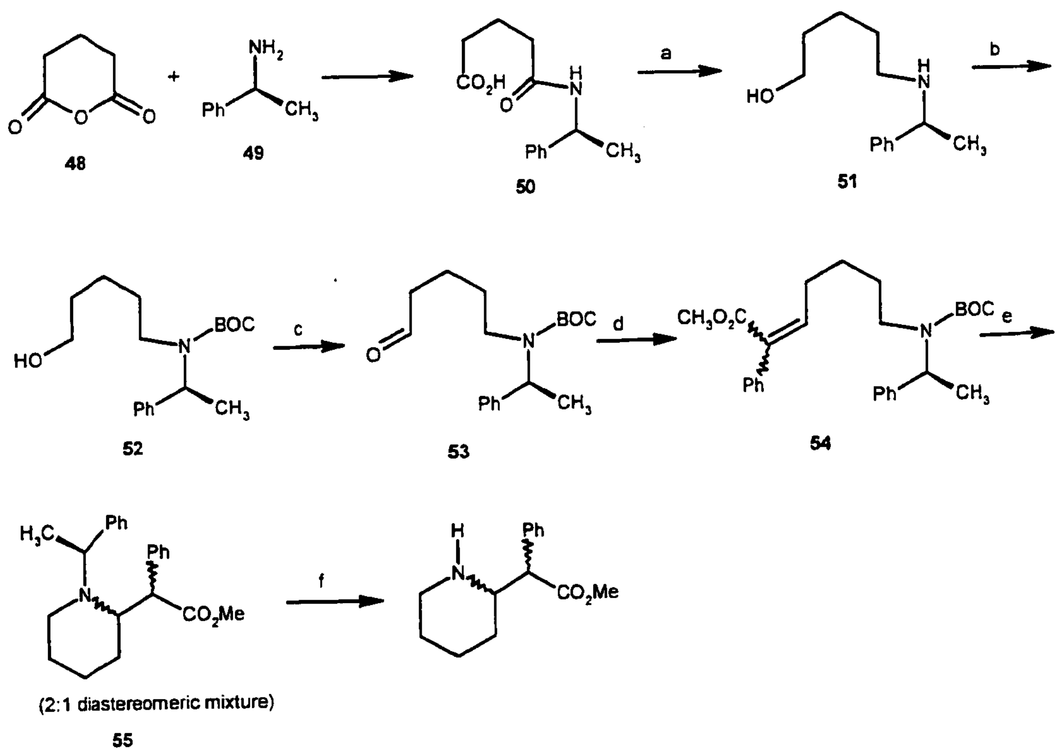
Fox et al.[41,42] reported an approach involving an intramolecular Michael addition as the key step (Scheme 14) and utilizing (*S*)-α-methylbenzylamine as the chiral auxiliary, towards a potential synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) free base. Ring opening of glutaric anhydride (48) with (*S*)-α-methylbenzylamine (49) furnished the acid 50. Reduction of 50 afforded the amino alcohol 51 in 78% yield. Protection of the secondary amine with $(BOC)_2O$ followed by Swern oxidation gave the alde-



(a) 2.3 F/mol of electricity in CH_3OH containing $(C_2H_5)_4NBF_4$, (85%) (b) $TiCl_4$, DIPEA, CH_2Cl_2, −78 °C to RT; (c) LiOOH, THF–water, RT; (d) CH_2N_2, ether, RT (54% from **45**); (e) $(CH_3)_3SiI$, CH_2Cl_2, RT (75%).

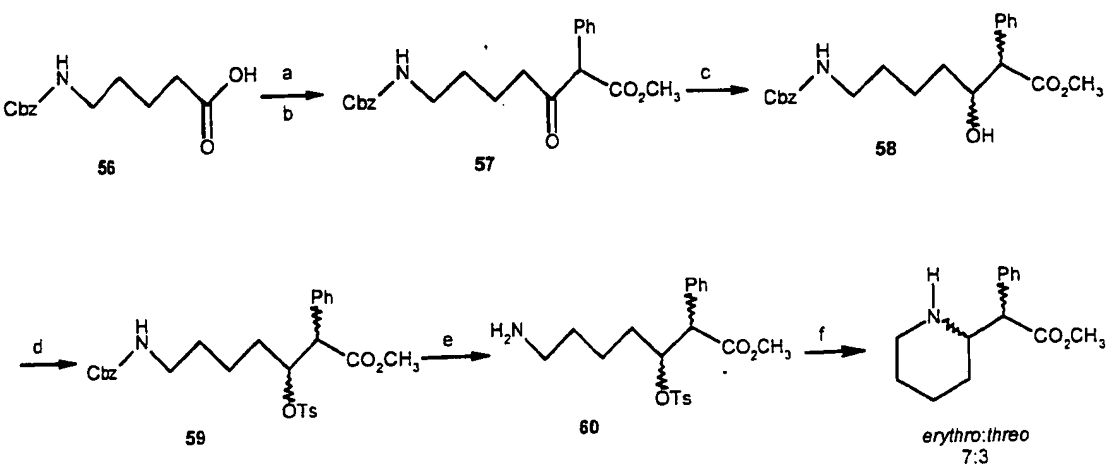
Scheme 13.

hyde 53 in 68% yield. Horner-Wadsworth-Emmons olefination of 53 afforded the α,β-unsaturated ester 54 as a mixture of geometrical isomers. Treatment of 54 in the presence of lithium diethylamide in THF led to the cyclization of only one regioisomer to give a 2:1 mixture of diastereomers 55. As four diastereomers



(a) reduction (78%); (b) $(BOC)_2O$, THF–2 M NaOH (89%); (c) DMSO, oxalyl chloride, $(C_2H_5)_3N$ (68%); (d)(i) methyl 2-bromophenylacetate, triethylphosphite (ii) NaHMDS, THF (66%); (e) (i) TFA (ii) $(C_2H_5)_3N$ (iii) lithium diethylamide, THF, –78 °C; (f) hydrogenation.

Scheme 14.



(a) *N,N'*-carbonyldimidazole, THF; (b) $PhCH_2CO_2CH_3$, LDA (66.4%); (c) [RuI(*p*-cymene)(S)-binap]I, cat. tin chloride, camphor-10-sulfonic acid, H_2, CH_3OH, 80 °C (87.4%); (d) *p*-toluenesulfonyl chloride, pyridine, cat. DMAP (61.8%); (e) H_2, 5% Pd-C; (f) K_2CO_3, CH_3OH (77.5%).

Scheme 15.

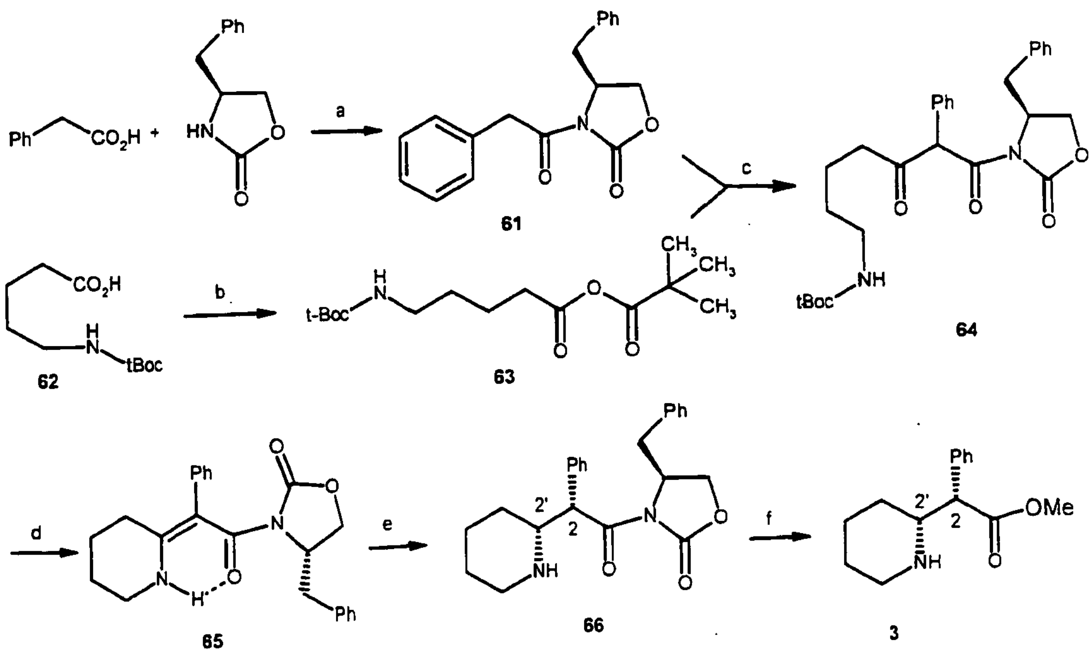
could be produced in this cyclization, this represents good distereoselectivity. The diastereomeric mixture 55 was hydrogenated to afford a diastereomeric mixture of 1. Neither the enantiomeric purity nor the characterization of the diastereomers was reported.

Another potential approach towards 1 was reported by Seido et al.[43] utilizing an asymmetric reduction of the ketone (57; Scheme 15) as the key step. Acylation of the lithium enolate of methyl phenylacetate with the imidazolide, obtained by treatment of the acid 56 with *N,N'*-carbonyldiimidazole, gave the ketoester 57 in 66.4% yield. Asymmetric reduction of 57 with [RuI(*p*-cymene)(*S*)-binap]I, tin chloride, and camphor-10-sulfonic acid in methanol at 80 °C afforded the alcohol 58 as a mixture of *syn* and *anti* forms in 87.4% yield. The ratio of *syn* to *anti* isomers was 76.3:23.7 and the enantiomeric purity of each form was 95.6% ee and 97.8% ee, respectively. Tosylation of 58 with *p*-toluenesulfonyl chloride and pyridine in the presence of catalytic amounts of DMAP yielded a diastereomeric mixture of tosylate 59 in 61.8% yield. Deprotection of the *N*-Cbz group in 59 by hydrogenation over 5% Pd-C followed by cyclization of the resulting amino tosylate 60 with potassium carbonate in methanol furnished methylphenidate as a mixture of *erythro* and *threo* isomers in a 7:3 ratio and 77.5% yield.

7 Approaches Based on Enantioselective Synthesis of (2*S*,2'*R*)-*erythro*-Methylphenidate and Epimerization

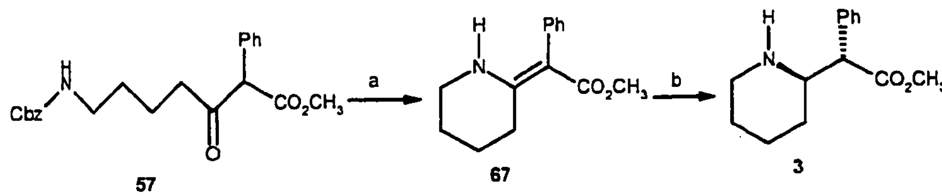
Because epimerization of (2*S*,2'*R*)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (12; Scheme 2) at the benzylic stereogenic center is known to afford (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (13), enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate (3) would provide a feasible approach to (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) after epimerization.

We (Novartis) reported[44] an enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate (3) utilizing Evans (*S*)-4-benzyl-2-oxazolidinone chiral auxiliary to control the diastereofacial selectivity in the hydrogenation of enamine intermediate (65; Scheme 16). Acylation of (*S*)-4-benzyl-*N*-phenylacetyl-2-oxazolidinone (61) with the mixed anhydride 63, followed by deprotection of the *N*-Boc group with TFA, and neutralization of the reaction mixture with $NaHCO_3$ afforded the enamine intermediate 65. Hydrogenation of enamine 65 with 10% Pd-C in ethyl acetate furnished 66 in 95% yield with an excellent diastereoselectivity (97:3). Treatment of 66 with methanol in the presence of LnI_3 afforded the desired



(a) *t*-BuCOCl, Et_3N, $PhCH_3$, 80 °C, 12 h (85%); (b) *t*-BuCOCl, Et_3N, $PhCH_3$, RT, 4 h (100%); (c) LiHMDS, THF, –78 °C to RT, 4 h; (d) i) TFA, CH_2Cl_2, 0 °C to RT, 4 h, ii) $NaHCO_3$ (30% in two steps); (e) 10% Pd-C, EtOAc, RT, 24 h (95%); (f) MeOH, LnI_3, THF, RT, 16 h (85%).

Scheme 16.



(a) H_2, 5% Pd/C, CH_3OH (93.9%); (b) H_2, [RuI(p-cymene)((*R*)-H8-binap)], CH_3OH, HCl, 50 °C (98.7%).

Scheme 17.

(2*S*,2'*R*)-*erythro*-methylphenidate (3) in 85% yield. The enantiomeric purity of 3 was excellent (2*S*,2'*R*:2*R*,2'*S* = 97:3).

Another synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate (3) was reported by Seido et al.[45] involving asymmetric hydrogenation of enamine 67 as the key step (Scheme 17). Deprotection of the *N*-Cbz group in ketoester 57 by hydrogenation over 5% Pd-C gave the enamine 67 in 95% yield. Asymmetric hydrogenation of 67 with [RuI(*p*-cymene)((*R*)-H8-binap)] in methanol containing HCl at 50 °C furnished (2*S*,2'*R*)-*erythro*-methylphenidate (3) in 98.7% yield and the ratio of *erythro* to *threo* diastereomers was 99:1. The enantiomeric purity of the *erythro* isomer was 99.4% ee. Hydrogenation using (*R*)-Tol-BINAP as the ligand afforded a mixture of *erythro* and *threo* isomers in a 99.1:0.9 ratio, respectively, which was epimerized to a 26.6:73.4 mixture of *erythro* to *threo* isomers, respectively, with 88.8% ee of the *threo* isomer.

8 Conclusions

After the first preparation of enantiomerically pure (2*R*,2'*R*)-*threo*-methylphenidate hydrochloride (1) in 1958, it is only recently that a great deal of interest has been demonstrated in the synthesis of this molecule. Various approaches to the preparation of enantiomerically pure (2*R*,2*R*)-(+)-*threo*-methylphenidate hydrochloride (1) are reviewed. These approaches include synthesis using enantiomerically pure precursors obtained by resolution, classical and enzyme-based resolution approaches, enantioselective synthesis approaches, and approaches based on enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate followed by epimerization at the 2-position. Classical resolution approaches have been successfully upscaled to produce 1 on a multi-kilogram scale due to the ready availability of racemic (±)-*threo*-methylphenidate hydrochloride (**10**). While some enantioselective approaches are short, they do not provide 1 of the desired enantiomeric purity necessary for drug development. Enantioselective synthesis approaches to produce 1, however, will become viable, particularly those based on approaches reported by us (Novartis),[35] Matsumura,[39,40] and Seido.[45]

Acknowledgements

I would like to thank Drs. Oljan Repič, Thomas J. Blacklock, Bin Hu, Hong-Yong Kim, Yugang Liu, and Mr. Denis Har and Mr. Yansong Lu for their contributions and help in preparing this review article.

References

[1] L. Hechtman, *Psychiatr. Clin. North Am.* **1992**, *1*, 553–565.
[2] R. A. Barkley, *Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment*, Guilford Press: New York, **1990**.
[3] P. S. Jensen, R. A. C. Irwin, A. D. Josephson, *J. Am. Acad. Child Adolesc. Psychiatry* **1996**, *35*, 55–66.
[4] J. G. Millichap, *Ann. N. Y. Acad. Sci.* **1973**, *205*, 321.
[5] J. M. Swanson, M. Kingsbourne in *Attention and Cognitive Development*, Eds. G. H. Hale, M. Lewis, Plenum Press: New York, **1979**, pp. 249.
[6] A. L. Zeitlin, M. M. Dariani, D. I. Stirling, *US Patent* 5,908,850, **1999**.
[7] K. S. Patrick, R. W. Caldwell, R. M. Ferris, G. R. Breese, *J. Pharm. Exp. Ther.* **1987**, *241*, 152–158.
[8] Y. S. Ding, J. S. Fowler, N. D. Volkow, S. L. Dewey, G. J. Wang, J. Logan, S. J. Gatley, N. Pappas, *Psychopharmacology* **1997**, *131*, 71–78.
[9] X. Weng, Y. S. Ding, N. D. Volkow, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 11073–11074.
[10] L. Panizzon, *Helv. Chim. Acta* **1944**, *27*, 1748–1756.
[11] M. Hartmann, L. Panizzon, *US Patent* 2,507,631, **1950**.
[12] R. Rometsch, *US Patent* 2,838,519, **1958**.
[13] R. Rometsch, *US Patent* 2,957,880, **1960**.
[14] R. A. Maxwell, E. Chaplin, S. B. Eckhardt, J. R. Soares, G. Hite, *J. Pharmacol. Exp. Ther.* **1970**, *173*, 158–165.
[15] H. Egger, F. Bartlett, R. Dreyfuss, J. Karliner, *Drug Metabolism and Disposition* **1981**, *9*, 415–423.
[16] H. M. Deutsch, Q. Shi, E. Gruszeck-Kowalik, M. M. Schweri, *J. Med. Chem.* **1996**, *39*, 1201–1209.
[17] J. M. Axten, L. Krim, H. F. Kung, J. D. Winkler, *J. Org. Chem.* **1998**, *63*, 9628–9629.

[18] J. D. Winkler, J. A. Axten, L. Krim, *World Patent Application No.* WO 99/36403, 1999.
[19] L. C. Dias, M. A. dePiloto Fernandes, *Synth. Commun.* 2000, *30*, 1311–1318.
[20] M. Prashad, D. Har, O. Repič, T. J. Blacklock, P. Giannousis, *Tetrahedron: Asymmetry* 1998, *9*, 2133–2136.
[21] S. Faulconbridge, H. S. Zavareh, G. R. Evans, M. Langston, *World Patent Application No.* WO 98/25902, 1998.
[22] V. Khetani, Y. Luo, S. Ramaswamy, *World Patent Application No.* WO 98/52921, 1998.
[23] S. Ramaswamy, V. Khetani, *US Patent* 5,965,734, 1999.
[24] D. L. Thai, M. T. Sapko, C. T. Reiter, D. E. Bierer, J. M. Perel, *J. Med. Chem.* 1998, *41*, 591–601.
[25] V. Khetani, Y. Luo, S. Ramaswamy, *US Patent* 5,936,091, 1999.
[26] M. Langston, H. S. Zavareh, *World Patent Application No.* WO 97/28124, 1997.
[27] H. S. Zavareh, G. A. Potter, *World Patent Application No.* WO 98/31668, 1998.
[28] M. C. J. Harris, H. S. Zavareh, *World Patent Application No.* WO 97/27176, 1997.
[29] M. Prashad, B. Hu, O. Repič, T. J. Blacklock, P. Giannousis, *Org. Proc. Res. Dev.* 2000, *4*, 55–59.
[30] M. Prashad, B. Hu, *US Patent* 6,162,919, 2000.
[31] H. S. Zavareh, *World Patent Application No.* WO 97/32851, 1997.
[32] M. Prashad, D. Har, O. Repič, T. J. Blacklock, P. Giannousis, *Tetrahedron: Asymmetry* 1999, *10*, 3111–3116.
[33] M. Prashad, D. Har, *US Patent* 6,100,401, 2000.
[34] A. L. Zeitlin, D. I. Stirling, *US Patent* 5,733,756, 1998.
[35] M. Prashad, H. Y. Kim, Y. Lu, Y. Liu, D. Har, O. Repič, T. J. Blacklock, P. Giannousis, *J. Org. Chem.* 1999, *64*, 1750–1753.
[36] J. M. Axten, R. Ivy, L. Krim, J. D. Winkler, *J. Am. Chem. Soc.* 1999, *121*, 6511–6512.
[37] J. D. Winkler, J. M. Axten, L. Krim, *US Patent* 6,025,502, 2000.
[38] H. M. L. Davies, T. Hansen, D. W. Hopper, S. A. Panaro, *J. Am. Chem. Soc.* 1999, *121*, 6509–6510.
[39] Y. Matsumura, Y. Kanda, K. Shirai, O. Onomura, T. Maki, *Org. Lett.* 1999, *1*, 175–178.
[40] Y. Matsumura, Y. Kanda, K. Shirai, O. Onomura, T. Maki, *Tetrahedron* 2000, *56*, 7411–7422.
[41] M. E. Fox, J. M. Paul, *World Patent Application No.* WO 97/35836, 1997.
[42] M. E. Fox, J. M. Paul, *US Patent* 6,031,124, 2000.
[43] N. Seido, T. Nishikawa, T. Sotoguchi, Y. Yuasa, T. Miura, H. Kumobayashi, *US Patent* 5,801,271, 1998.
[44] M. Prashad, Y. Liu, H. Y. Kim, O. Repič, T. J. Blacklock, *Tetrahedron: Asymmetry* 1999, *10*, 3479–3482.
[45] N. Seido, T. Nishikawa, T. Sotoguchi, Y. Yuasa, T. Miura, H. Kumobayashi, *US Patent* 5,859,249, 1999.

APPENDIX E

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/34

A1

(11) International Publication Number: WO 97/28124

(43) International Publication Date: 7 August 1997 (07.08.97)

(21) International Application Number: PCT/GB97/00281

(22) International Filing Date: 31 January 1997 (31.01.97)

(30) Priority Data:

9602174.6	2 February 1996 (02.02.96)	GB
9618836.2	10 September 1996 (10.09.96)	GB

(71) Applicant: MEDEVA EUROPE LIMITED [GB/GB]; 10 St. James's Street, London SW1 1EF (GB).

(72) Inventors: LANGSTON, Marianne; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). ZAVAREH, Hooshang, Shahriari; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF D-THREO-(R,R)-METHYL PHENIDATE AND RECYCLING OF UNDESIRED ENANTIOMERS BY EPIMERISATION

(57) Abstract

A process for obtaining a single enantiomer, *d* or *l*, of *threo*-methylphenidate, comprises resolution of a mixture of the enantiomers; racemisation of the unwanted enantiomer, to give a mixture of all four stereoisomers; and separation of the *erythro* stereoisomers, to leave the said mixture of enantiomers for resolution.

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PROCESS FOR THE PREPARATION OF D-THREO-(R,R)-METHYL PHENIDATE AND RECYCLING OF UNDESIRED ENANTIOMERS BY EPIMERISATION

Field of the Invention

This invention relates to an economic process for the manufacture of a single isomer of methylphenidate.

Background to the Invention

Methylphenidate is a therapeutic agent that is widely used in the treatment of attention-deficit hyperactivity disorder. It is a controlled substance.

Methylphenidate was first prepared as a mixture of the *erythro* [*R***S**] and *threo* [*R***R**] racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereoisomer. It is now considered that it is the *d-threo* [or (*R,R*)] enantiomer that has the preferred therapeutic activity. Uses of this enantiomer are disclosed in PCT/GB96/01688, PCT/GB96/01689 and PCT/GB96/01690, the contents of which are incorporated herein by reference.

The resolution of *threo*-methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diylhydrogen phosphate, a process first reported by Patrick *et al*, The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987). A more efficient resolution, using a *O,O*'-diaroyltartaric acid, is disclosed in PCT/GB97/00185, the contents of which are incorporated by reference; in particular, the use of *O,O*'-di-*p*-toluoyltartaric acid allows the diastereoisomeric salts to be very readily separated.

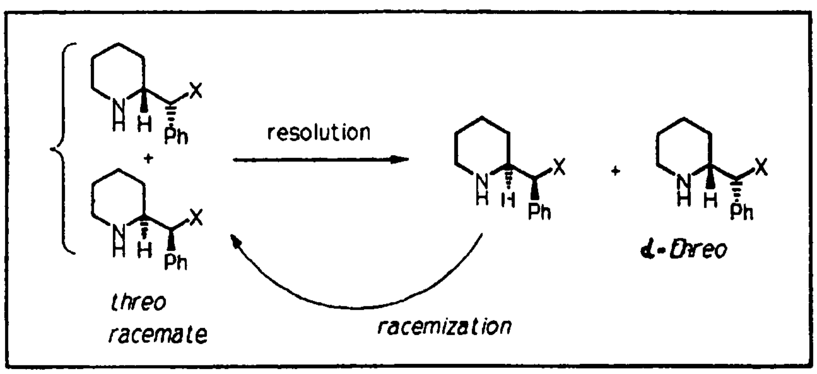
In an alternative approach, disclosed in US-A-2957880, the amide of *erythro*-methylphenidate (i.e. as -$CONH_2$ instead of -CO_2Me) is resolved using tartaric acid. However, this resolution must be followed by amide hydrolysis, and equilibration at the benzylic centre, to give the *threo* isomer of the carboxylic acid (ritalinic acid) which is esterified. US-A-2957880 describes a general process for conversion of *erythro* diastereoisomers to *threo* diastereoisomers, using alkali and elevated temperature.

In order to establish an economic resolution process, it is highly desirable to be able to recycle the unwanted enantiomer into the resolution by way of a racemisation. This becomes especially important when the resolution is performed late in a synthesis. An example of such a resolution and racemisation procedure is

in the case of naproxen where the single stereogenic carbon centre, which is benzylic and further activated by the carboxylate, is readily racemised. However, in the case of methylphenidate, there are two stereogenic centres. While one centre is similarly benzylic and can be epimerised as indicated in US-A-2957880, that converts the material into a mixture of two diastereoisomers and not into the racemate that is required for recycling.

Summary of the Invention

This invention is based on the discovery of methods to effect racemisation of both chiral centres of methylphenidate. This process gives an optically inactive mixture of stereoisomers in which equilibrium may favour the *threo* isomer; the result is that undesired enantiomer is converted predominantly into the racemate of the *threo* isomer which can then be reintroduced into the resolution. The overall process of a combination of resolution and racemisation that may allow complete conversion into the required isomer is outlined in Scheme 1. The *erythro* isomer that may remain after the racemisation can be separated by conventional methods such as crystallisation at this stage and subjected further to the epimerisation conditions defined below. Alternatively, it can be recycled after passage through resolution of the *threo* isomer.



Scheme 1

Description of the Invention

In Scheme 1, the group X may be the $-CO_2Me$ function of methylphenidate. Resolution of this compound may be carried out by generally known procedures, e.g. by formation of a diastereoisomeric salt with a chiral acid. Alternatively, the resolution may be a biotransformation that modifies the group X in one enantiomer so that the enantiomers (of different compounds) are then readily separated.

This invention includes the means to effect racemisation at both stereogenic centres. It has been discovered that such racemisation can be carried out by way of activation at the piperidine nitrogen, which probably promotes a fragmentation of the ring, although the exact mechanism has not been ascertained. The putative olefinic intermediate has no chirality and recloses to a racemic mixture.

There are various ways in which the nitrogen may be activated, to promote the elimination-addition mechanism. One approach is treatment with an acid, for example a carboxylic acid, at a sufficiently high temperature, such as heating with propionic acid, e.g. under reflux. This reaction is suitably conducted in an inert solvent such as toluene. The racemisation can optionally be accelerated by the judicious addition of amounts of additives such as water or inorganic salts that will favour the charge separation in the transition state of the elimination. This reaction may also be promoted by the addition of an aldehyde or ketone (e.g. butyraldehyde or 2-cyclohexen-1-one).

As indicated above, conditions are known that will epimerise *erythro*-ritalinic acid at the benzylic centre only. On the basis of the evidence herein, it will readily be apparent to the man of ordinary skill in the art that conditions can be adopted, in order to give all 4 stereoisomers of methylphenidate, by racemisation at both chiral centres.

Following racemisation, and prior to resolution, it is necessary to enrich the mixture in the *threo* enantiomers. For example, the racemic methylphenidate is hydrolysed, e.g. using base such as alkali metal hydroxide. This can be done such that there is also epimerisation. Work-up with acid gives predominantly *threo* ritalinic acid ($X = CO_2H$), which can be esterified, e.g. by reaction with methanol, to give the appropriate substrate for resolution.. Alternatively, the *erythro* isomers

can be separated by precipitation, and then subjected to sequential epimerisation, esterification and resolution.

The following experiment was conducted in order to illustrate the feasibility of racemisation.

Propionic acid (2 ml) was added to a solution of *d-threo*-methylphenidate (5 g) in toluene (25 ml), and the solution was heated under reflux for 4 hours. The mixture was then cooled to ambient temperature, and was rinsed with dilute sodium carbonate and then with water. The organic phase was separated and dried with magnesium sulphate and evaporated under reduced pressure. The resulting oil (4.3 g) was analysed by chiral HPLC which indicated the presence of all 4 stereoisomers of methylphenidate in roughly equal proportions.

In order to preparing *d-threo*-methyphenidate by an efficient recycling process, the following protocol is adopted:

1) Resolve *dl-threo*-methylphenidate by the procedure described in the Example of PCT/GB97/00185.
2) Racemise the residual *l-threo*-methylphenidate by the procedure described in the experiment above.
3) Hydrolyse the resultant racemic methylphenidate using 50% KOH and heating at reflux.
4) Esterify the resultant mixture of enantiomers, enriched in *dl-threo*-ritalinic acid, by reaction with MeOH and HCl.
5) Isolate the free base and recrystallise, to obtain essentially pure *dl-threo*-methylphenidate, suitable as a feedstock for resolution into constituent enantiomers.

CLAIMS

1. A process for obtaining a single enantiomer, *d* or *l*, of *threo*-methylphenidate, which comprises resolution of a mixture of the enantiomers; racemisation of the unwanted enantiomer, to give a mixture of all four stereoisomers; and separation of the *erythro* stereoisomers, to leave the said mixture of enantiomers for resolution.

2. A process according to claim 1, wherein the single enantiomer obtained is the *d-threo* isomer, i.e. the isomer of (*R*,*R*) absolute configuration.

3. A process according to claim 1 or claim 2, wherein the racemisation comprises heating the unwanted enantiomer with a carboxylic acid.

4. A process according to any preceding claim, wherein the separation is conducted following hydrolysis of the mixture of stereoisomers, to give ritalinic acid, and before or after re-esterification of the acid.

5. A process according to claim 4, which additionally comprises equilibrating the product of hydrolysis such that the *threo* diastereoisomer is preferentially obtained.

6. A process according to any preceding claim, wherein the resolution is conducted using a chiral acid.

7. A process according to claim 6, wherein the acid is *O,O'*-diaroyltartaric acid.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00281

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2 957 880 A (R. ROMETSCH) 25 October 1960 cited in the application see the whole document ---	1-7
A	J. ORG. CHEM., vol. 48, no. 6, 1983, pages 843-846, XP000604702 S. YAMADA ET. AL.: "Method for the Racemization of Optically Active Amino Acids" see the whole document ---	1-7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
8 April 1997	16.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Kissler, B

Form PCT/ISA/210 (second sheet) (July 1992)